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Michel T. Halbouty Energy Co.

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University of Wisconsin

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University of Utah

JOSEPH E. ROSS
Congressional Research Service

LEWIS THOMAS
Memorial Sloan-Kettering Cancer Center

Director

JOHN H. GIBBONS

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New Developments in Biotechnology

1

Ownership of Human Tissues and Cells

CONGRESS OF THE UNITED STATES
Office of Technology Assessment
Washington, DC 20510-8025

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Foreword

In the 1960s, the term "biotechnology" did not exist. In the 1970s, development of techniques for: 1) splicing genetic information of one organism into that of another, and 2) fusing cells to produce large quantities of valuable proteins led to recognition that a revolution in biological technology—that is, *biotechnology*—was at hand. In the 1980s, biotechnology is best viewed as a growing cohort of technologies, each with its own scientific benefits and risks, and allied social, economic, legal, and ethical issues.

In this special report, OTA analyzes the economic, legal, and ethical rights of the human sources of tissues and cells and also those of the physicians or researchers who obtain and develop these biological materials. The study describes the potential of three rapidly moving technologies (tissue and cell culture, cell fusion to produce monoclonal antibodies, and recombinant DNA) for manipulating human tissues and cells to yield commercially valuable products. The report includes a range of options for congressional action related to commercialization of human biological materials, regulation of research with human subjects, and disclosure of physicians' commercial interest in patient treatment.

This special report is the first in a series of OTA studies being carried out under an assessment of "New Developments in Biotechnology." Forthcoming reports will include evaluations of: U.S. investment in biotechnology; public attitudes toward biotechnology; genetic and ecological issues in the environmental release of genetically engineered organisms; and the impact of intellectual property law on biotechnology. The assessment was requested by the House Committee on Science and Technology and the House Committee on Energy and Commerce.

OTA was assisted in preparing this study by an advisory panel, a workshop group, and reviewers selected for their expertise and diverse points of view on the issues covered in the report. OTA gratefully acknowledges the contribution of each of these individuals. As with all OTA reports, responsibility for the content of the special report is OTA's alone. The special report does not necessarily constitute the consensus or endorsement of the advisory panel, the workshop group, or the Technology Assessment Board.

John H. Gibbons

JOHN H. GIBBONS
Director

New Developments in Biotechnology Advisory Panel

Bernadine P. Healy, *Panel Chair*
The Cleveland Clinic Foundation
Cleveland, OH

Timothy B. Atkeson
Steptoe & Johnson
Washington, DC

David Blumenthal
Brigham and Women's Hospital Corp.
Boston, MA

Hon. Edmund G. Brown, Jr.
Reavis & McGrath
Los Angeles, CA

Nancy L. Buc
Weil, Gotshal & Manges
Washington, DC

Mark F. Cantley
Concertation Unit for Biotechnology in Europe
Brussels, Belgium

Alexander M. Capron
University of Southern California
Los Angeles, CA

Jerry D. Caulder
Mycogen Corporation
San Diego, CA

Lawrence I. Gilbert
The University of North Carolina
Chapel Hill, NC

Conrad A. Istock
The University of Arizona
Tucson, AZ

Edward L. Korwek
Keller and Heckman
Washington, DC

Tsune Kosuge
University of California, Davis
Davis, CA

Richard Krasnow
Resources for the Future
Washington, DC

Sheldon Krimsky
Tufts University
Medford, MA

Joshua Lederberg
The Rockefeller University
New York, NY

William E. Marshall
Pioneer Hi-Bred International, Inc.
Johnston, IA

Ronald L. Meeusen
Rohm and Haas Company
Spring House, PA

Robert B. Nicholas
Blum, Nash & Railsback
Washington, DC

Eric J. Stanbridge
University of California, Irvine
Irvine, CA

James M. Tiedje
Michigan State University
East Lansing, MI

Kunio Toriyama
ZEN-NOH
Tokyo, Japan

Pablo D.T. Valenzuela
Chiron Corporation
Emeryville, CA

Thomas E. Wagner
Ohio University
Athens, OH

Luther S. Williams
Atlanta University
Atlanta, GA

NOTE: OTA appreciates and is grateful for the valuable assistance and thoughtful critiques provided by the panel members. The panel members do not, however, necessarily approve, disapprove, or endorse this report. OTA assumes full responsibility for the report and the accuracy of its contents.

Ownership of Human Tissues and Cells—OTA Project Staff

Roger C. Herdman, *OTA Assistant Director*
Health and Life Sciences Division

Gretchen S. Kolsrud, *Biological Applications Program Manager*

Gary B. Ellis, *Project Director*

Gladys B. White, *Study Director* and *Analyst*

Lisa J. Raines, *Study Director* and *Legal Analyst*[1]

Robyn Y. Nishimi, *Analyst*

Kevin W. O'Connor, *Legal Analyst*

Support Staff

Sharon Kay Oatman, *Administrative Assistant*

Linda S. Rayford, *Secretary/Word Processing Specialist*

Barbara V. Ketchum, *Clerical Assistant*

Editor

Chris Elfring, Takoma Park, MD

Outside Contributors

James F. Childress, University of Virginia
Iver P. Cooper, Mackler, Cooper and Marx
Jeffrey N. Gibbs, Mackler, Cooper and Marx
Bruce G. Goodman, Damon Corporation
Warren Greenberg, George Washington University
Rosemary Gibson Kern, American Enterprise Institute
Patricia A. King, Georgetown University
Gilah Langner, ICF, Inc.
Robert J. Levine, Yale University
Mark J. Minasi, Moulton & Minasi
Thomas H. Murray, University of Texas Medical Branch, Galveston
Fay A. Rozovsky, Halifax, Nova Scotia
Emanuel Thorne, Washington, DC
Allen B. Wagner, Berkeley, CA

Acknowledgment to Other OTA Staff

Clyde J. Behney, *Health Program, Manager*
R. Alta Charo, *Legal Analyst*
Kathi E. Hanna, *Analyst*
Jane E. Sisk, *Senior Associate*

---

[1] Through May 1986.

New Developments in Biotechnology
Working Group on Ownership of Human Tissues and Cells

LeRoy Walters, *Working Group Chair*
Georgetown University
Washington, DC

Thomas L. Beauchamp
Georgetown University
Washington, DC

Bruce G. Goodman
Damon Corporation
Needham Heights, MA

Geoffrey M. Karny
Finnegan, Henderson, Farabow, Garrett and Dunner
Washington, DC

Patricia A. King
Georgetown University Law Center
Washington, DC

Robert J. Levine
Yale University School of Medicine
New Haven, CT

Charles R. McCarthy
National Institutes of Health
Bethesda, MD

Barbara Mishkin
Hogan & Hartson
Washington, DC

Thomas H. Murray
University of Texas Medical Branch
Galveston, TX

Joseph G. Perpich
Meloy Laboratories, Inc.
Springfield, VA

Ivor Royston
University of California, San Diego
San Diego, CA

Herbert F. Schwartz
Fish & Neave
New York, NY

Howard S. Schwartz
Jewish General Hospital
Montreal, Quebec

OTA is grateful for the valuable assistance and thoughtful critiques provided by the Working Group members. The views expressed in this OTA report, however, are the sole responsibility of the Office of Technology Assessment.

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Chapter 1

Summary, Policy Issues, and Options for Congressional Action

HUMAN BIOLOGICAL MATERIALS: QUESTIONS FOR THE FUTURE

New developments in biotechnology hold great promise for advancing knowledge about various life forms and improving human health. But with this promise come greater responsibilities for scientists and policymakers. Human biological materials—tissues and cells—can be used to develop commercial products (e.g., hybridomas and cultured cell lines[1]), and for diagnostic and therapeutic purposes. The use of human biological materials for therapy, research, and profit raises important legal, ethical, and economic issues (see table 1).

Many of these issues are similar to those that have been raised concerning human organ donation, which is currently regulated as a result of the Uniform Anatomical Gift Act (National Conference of Commissioners on Uniform State Laws, 1968) and the 1984 National Organ Transplant Act (Public Law 98-507). But the use of human tissues and cells in biotechnology raises questions that have not been answered in previous public policy deliberations concerning the acquisition of human organs. **Who owns a cell line—the human source of the original tissues and cells or the scientist who developed the cell line? Should biological materials be sold, and if so, what are the implications for equity of distribution? Should disclosure, informed consent, and regulatory requirements be modified to cope with the new questions raised by the increased importance and value of human biological materials?** There are no easy answers. These issues are novel and complex, and no single body of law, policy, or ethics applies directly.

Table 1.—Human Biological Materials: Many Questions, Few Definitive Answers

- Are bodily substances "property" to be disposed of by any means one chooses, including donation or sale?
- Do property rights to their genetic identity adhere to individuals or to the species?
- Who should make the basic decisions affecting the acquisition of tissues and cells, and under what circumstances should such acquisition be permitted or denied?
- What are patients and research subjects entitled to know about the potential for commercial exploitation of an invention that uses their bodily materials? And what is the probability that an individual's tissues and cells will end up in a commercial product?
- How is it that inventions incorporating human cells are patentable in the first place? How similar is the invention to the original biological material?
- What is the nature of the researcher's contribution versus the source's contribution to the invention?
- Who should profit from federally funded research using human tissue? To what extent are the issues raised by ownership of human biological materials related to commercial relationships between universities and companies?
- What are the implications of these issues for scientists, physicians, patients, volunteer research subjects, universities, and the biomedical product industry?

SOURCE: Office of Technology Assessment, 1987.

Definitions

Human bodies contain a number of elements that are useful in biomedical research. Healthy people continually produce a variety of replenishable substances, including blood, skin, bone marrow, hair, urine, perspiration, saliva, milk, semen, and tears. Human bodies also contain nonreplenishing parts, such as organs or oocytes. Organs may be either vital (e.g., heart) or to some extent expendable (e.g., lymph nodes or a second kidney). Finally, the body can also have diseased parts. **While this report refers to all human parts—replenishing and nonreplenishing, living and nonliving, beneficial and detrimental—collectively as human biological materials, it focuses**

---

[1] *A hybridoma* is a hybrid cell resulting from the fusion of a particular type of immortal tumor cell line, a myeloma, with an antibody producing B lymphocyte. Cultures of such cells are capable of continuous growth and specific, monoclonal antibody production. A *cell line* is a sample of cells, having undergone the process of adaptation to artificial laboratory cultivation, that is now capable of sustaining continuous, long-term growth in culture.

Box A.—The Hagiwara Case: An Example of a Dispute Over Human Biological Materials

In early 1981, a researcher at the University of California, San Diego, was developing human hybridoma cell lines that would secrete antibodies to cancer cells. Learning of the project, Dr. Heideaki Hagiwara suggested the use of lymph cells from his mother, who was suffering from cervical cancer. The researcher agreed, and the Hagiwara cells were fused to an immortal cell line developed and patented by the investigator. A hybridoma that secreted an anti-tumor antibody was found.

Without the investigator's permission, Hagiwara took a subculture of the hybridoma cell line with him to Japan and gave it to the Hagiwara Institute of Health, directed by his father. The University and the Hagiwaras subsequently executed an agreement that permitted the Hagiwaras to use the cell line for scientific research but forbade their transfer to any other party for commercial purposes.

Several months later, the Hagiwaras asserted rights to the cell line and antibody, claiming that they had tangible property rights in the original tissue and were therefore entitled to a pecuniary interest in the derivative cell line. In 1983, the parties reached an agreement under which the University retained all patent rights and the Hagiwaras received an exclusive license to exploit the patent in Asia.

SOURCE: Office of Technology Assessment, 1987.

primarily on those biological materials most frequently used in biotechnology: tissues and cells. The terms specimens, body parts, human tissue, fluids, bodily substances, and biologicals are also used. **OTA distinguishes these undeveloped human biological materials from the biological inventions developed from them (and in some cases patented) such as cell lines, hybridomas, and cloned genes.**

The Problem of Uncertainty

At present, there is great uncertainty about how courts will resolve disputes between the human sources of specimens and specimen users. This could be detrimental to both academic researchers and the nascent biotechnology industry, particularly if the rights of a human source are asserted long after the specimen was obtained. The assertion of rights by human sources would affect not only the researcher who obtained the original specimen, but other researchers as well because biological materials are routinely distributed to other researchers for experimental purposes. Thus, scientists who obtain cell lines or other specimen-derivative products (e.g., gene clones) from the original researcher might also be sued. Furthermore, because inventions containing biological materials can be patented and licensed for commercial use, companies are unlikely to invest in developing, manufacturing, or marketing a product when uncertainty about clear title exists.

This uncertainty about the rights of specimen sources and specimen users could have far-reaching implications as research and development progresses. Research using human biological materials could be thwarted if universities and companies have difficulty obtaining title insurance covering ownership of cell lines or gene clones, or liability insurance. Insurers would be concerned not only with suits by individuals who can be identified as the sources of specimens, but also by the potential for class action lawsuits on behalf of all those who contributed specimens to a particular research project. Researchers generally claim that the pervasive use of human cells and tissues in biomedical research makes it impractical and inefficient to try to identify the sources of various specimens or to try to value their contributions. Regardless of the merit of these claims, however, resolving the current uncertainty may be more important to the future of biotechnology than resolving it in any particular way.

THE TECHNOLOGIES

Three broad classes of basic biological techniques are of particular relevance to this report. They are **tissue and cell culture technology, hybridoma technology, and recombinant DNA technology.**

Tissue and Cell Culture Technology

Cells are the basic structural unit of living organisms. A single cell is a complex collection of molecules with integrated functions forming a self-assembling, self-regulating entity. There are two broad classes of cells: prokaryotic and eukaryotic. Prokaryotes, generally considered to be the simpler of the two classes, include bacteria. Their genetic material is not housed in a separate structure (a nucleus) and the majority of prokaryotic organisms are unicellular. Eukaryotes are usually multicellular organisms; they contain a nucleus and other specialized structures to coordinate different cell functions. Human beings are eukaryotes.

Because eukaryotes are complex, scientists often study these organisms by examining isolated cells independent of the whole organism. This reductionist approach, called tissue and cell culture, is an essential technique for the study of human biological materials and the development of related biotechnologies. **Establishing human cell culture directly from human tissue is a relatively difficult enterprise and the probability of establishing a cell line from a given sample varies, ranging from 0.01 percent for some liver cells to nearly 100 percent for some human skin cells.**

Cell cultures isolated from nontumor tissue have a finite lifespan in the laboratory and most will die after a limited number of population doublings. These cultures will age (called senescence) unless pushed into immortality by outside interventions involving viruses or chemicals. The type of donor tissue involved and culture conditions are important variables of cell lifespan. Long-term growth of human cells and tissues is difficult, often an art. Most established cell cultures have been derived from malignant tissue samples. Tissue and cell culture techniques have greatly increased knowledge about cell biology and set the stage for the development of hybridoma technology.

Hybridoma Technology

In response to foreign substances, the body produces a constellation of different substances. Antibodies are one component of the immune response and they have a unique ability to identify specific molecules. Lymphokines, sometimes called bioregulators, are also produced during an immune response.

Cell culture technology provides the tools scientists need to produce pure, highly specific antibodies. By fusing two types of cells—an antibody-producing B lymphocyte with a certain tumor cell line (a myeloma)—scientists found that the resulting immortal hybrid cells, called hybridomas, secrete large amounts of homogeneous (or monoclonal) antibodies. Monoclonal antibodies have led to a greater understanding of the intricacies of the immune response and they have become powerful and widely used laboratory tools. They also have been approved for use as therapeutic agents. **Although the production of human monoclonal antibodies has proven much more difficult than the production of rodent monoclonal antibodies, the increasing availability of large supplies of monoclonal antibodies is revolutionizing research, commerce, and medicine.**

Lymphokines (e.g., interferon) were previously available in minute and usually impure amounts—if at all. Hybridoma, cell culture, and recombinant DNA technologies now permit lymphokines to be isolated in pure form and in quantities facilitating further analysis or use. The increased production and availability of these molecules has significant therapeutic promise in the treatment of a spectrum of diseases because of their exquisite specificity and reduced toxicity.

Recombinant DNA Technology

Recombinant DNA technology, also referred to as genetic engineering, involves the direct manipulation of the genetic material (the DNA) of a cell.

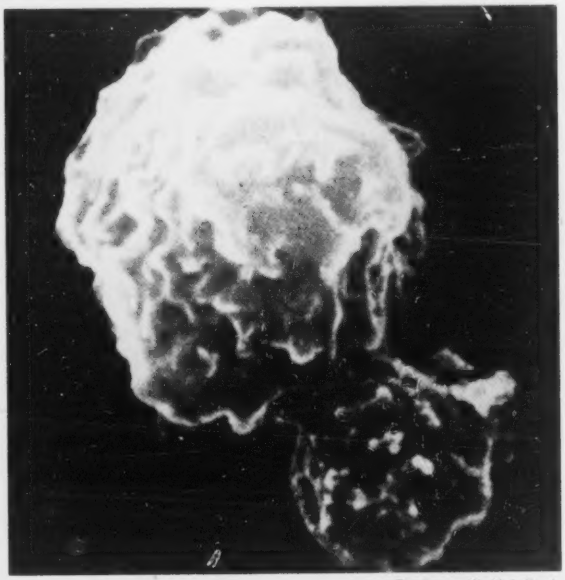


Photo credit: Hybritech

A mouse spleen cell and tumor cell fuse to form a hybridoma.

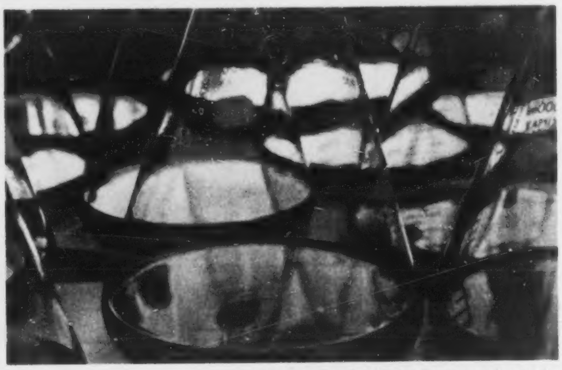


Photo credit: National Institutes of Health

Flasks filled with microbes that have been genetically engineered to produce interferon.

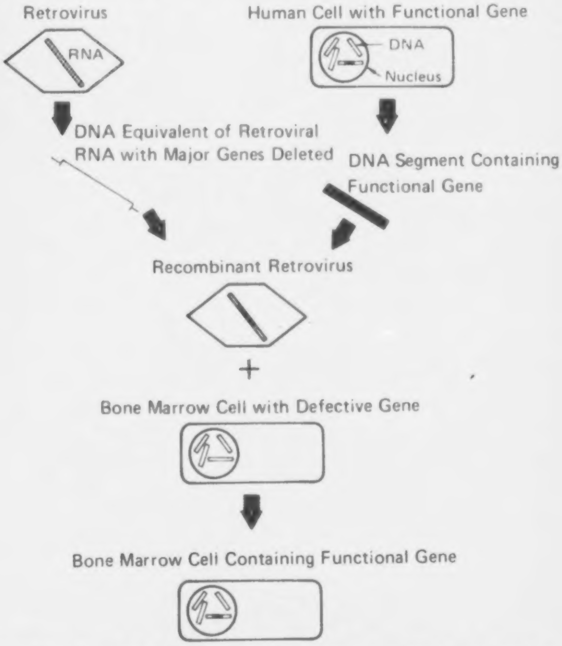
Using this technique, it is now possible to speed the isolation, examination, and development of a wide range of biological compounds. Like the use of cell culture, the use of recombinant DNA techniques has shed further light on the details of many important biological processes.

Gene cloning is a process that uses a variety of recombinant DNA procedures to produce multiple copies of a particular piece of genetic information. It is an important tool that accelerates the study or production of genes. All recombinant DNA methods require the following:

- a suitable vector to move DNA into the host cell,
- an appropriate host,
- a system to select and cull host cells that have received recombinant DNA, and
- a probe to detect the particular recombinant organisms of interest.

Recombinant DNA techniques have done much to illuminate the regulation and control of important human processes. In addition, advances in this technology underlie many commercial ventures to isolate or manufacture large quantities of scarce biological commodities.

Figure 1.—The Genetic Engineering of Human Cells


Retrovirus
RNA
Human Cell with Functional Gene
DNA
Nucleus
DNA Equivalent of Retroviral RNA with Major Genes Deleted
DNA Segment Containing Functional Gene
Recombinant Retrovirus
+
Bone Marrow Cell with Defective Gene
Bone Marrow Cell Containing Functional Gene

SOURCE: Steve Olson, *Biotechnology: An Industry Comes of Age*, prepared for the Academy Industry Program of the National Academy of Sciences/National Academy of Engineering/Institute of Medicine (Washington, DC: National Academy Press, 1986).

THE INTERESTED PARTIES

Although tissues and cells can be used for diagnostic, therapeutic, research, and commercial purposes, in fact the various uses of biological materials are usually intertwined, sometimes inextricably. This means that **a variety of people, including scientists in the research community (universities and industry), plus physicians, and patient and nonpatient sources, share an interest in the acquisition and use of human tissues and cells.** All would likely benefit from a resolution of the uncertainty surrounding the uses of biotechnology.

Commercial Interest in Human Biological Research and Inventions

The government has always maintained an interest in the legal, ethical, and economic implications of the research it is funding, and this interest is magnified when such research might result in inventions that are patentable under Federal law. In addition to advances in technology, **two events occurred in 1980 to precipitate the increasing research and commercial interest in human biological materials. First, the U.S. Supreme Court held for the first time that Federal patent law applies to new life forms created by DNA recombinations—opening up the possibility that products containing altered human cells and genes might also be patentable. Second, Congress amended the patent statute to encourage patenting and licensing of inventions resulting from government-sponsored research (Public Law 96-517).**

Even though the government is the primary source of funding for basic biomedical research, no single patent policy existed for government-supported research until 1980. Instead, each agency developed its own rules, resulting in 26 different patent policies. Under this system, only about 4 percent of some 30,000 government-owned patents were licensed. Furthermore, the government policy of granting nonexclusive licenses discouraged private investment, since a company lacking an exclusive license is reluctant to pay the cost of developing, producing, and marketing a product. Thus, potentially valuable research remained unexploited. To resolve this problem, Congress passed the Patent and Trademark Amendment Act in 1980 to prompt efforts to develop a uniform patent policy that would encourage cooperative relationships between universities and industry, and ultimately take government-sponsored inventions off the shelf and into the marketplace.

The changing legal climate has provided a fertile medium for the growth of university biomedical research and development using novel biotechnologies. **From 1980 through 1984, patent applications by universities and hospitals for inventions containing human biologicals increased more than 300 percent (compared to the preceding 5-year period). The extent to which these and forthcoming patents will be of commercial value is difficult to assess.**

Sources of Human Tissue

There are three major sources of specimens: patients, healthy research subjects, and cadavers.

- Patients are a source of both normal and atypical specimens and these individuals may or may not be research subjects. Patient-derived specimens may be "leftovers" obtained from diagnostic or therapeutic procedures and most human tissues or cells that find their way into research protocols are of this type. Patient-derived samples can also be provided as part of a research protocol.
- Healthy volunteer research subjects may donate replenishing biologicals if specimen removal involves little or no risk of harm, according to generally accepted principles of human subject research.
- Cadavers are the only permissible source of normal and atypical vital organs (including the brain, heart, and liver, but excluding kidneys and corneas). They are also the only permissible source of healthy benign organs (e.g., corneas) destined for research rather than transplantation.

While these donor classifications may seem fairly straightfoward, the human relationships involved are more dynamic than these categories suggest. In particular, the physician-patient relationship may change over the course of time into a researcher-subject relationship.

The Research Community

Research uses of human tissue are diverse and difficult to categorize. Generally, researchers are studying the characteristics and functions of healthy and diseased organs, tissues, and cells. Commercial products developed from human specimens are usually related to medical or research uses. The use of human biologicals is widespread; a recent survey conducted by the House Committee on Science and Technology found that 49 percent of the researchers at the medical institutions surveyed used patients' tissues or fluid in their research.

The revolutionizing effect of biotechnology on the use of human specimens is principally due to three factors:

- isolation of increasingly smaller amounts of important naturally occurring human biological factors (also known as biopharmaceuticals, bioresponse modulators, or biological mediators);
- production of virtually unlimited quantities of these factors (usually found in the body in only small amounts) using recombinant DNA methods; and
- discovery of techniques to create hybridomas, making it possible to generate large, pure supplies of specific antibodies.

At the most fundamental scientific level, human material is a source for studies designed to understand basic biological processes. From this basic research, commercial development may follow. However, **the probability that any one person's biological materials will be developed into a valuable product is exceedingly small. Thus, the issue of great potential commercial gain from donated materials is relevant to a small minority of sources**. However, in the future—as biotechnology progresses—the importance of the issue and the number of people involved could increase. The potential for commercial gain, while to date mostly a speculative consideration, could quickly become a reality. It is appropriate to consider these issues and the possible roles of the interested parties now, in advance of their becoming highly visible, so that public policy perspectives can be developed with wisdom and foresight.

Industry

The biotechnology industry is a major interested party in the controversy surrounding the use of human tissues and cells for financial gain. It is comprised of a variety of different types of organizations including the established pharmaceutical companies, oil and chemical companies, agricultural product manufacturers, and the new biotechnology companies. Of the nearly 350 commercial biotechnology firms in the United States actively engaged in biotechnology research and commercial product development, approximately 25 to 30 percent are engaged in research to develop a human therapeutic or diagnostic reagent. There is a strong international component to the biotechnology industry, with numerous research and development arrangements and partnerships between American firms and firms in Japan and Europe.

Photo credit: U.S. Department of Agriculture

Researcher withdraws a cell line sample from a freezing device.

LEGAL CONSIDERATIONS

United States law has long protected people from injury and damages. Much of this protection is afforded by the common law, the body of judge-made law built on judicial precedents. This body of legal principles has evolved over centuries as judges are called on to resolve disputes that have not been addressed by statute. Congress and State legislatures, however, have enacted numerous statutes to codify, modify, or overrule the common law, or to address larger societal issues that are inaccessible through the use of common law.

The common law does not provide any definitive answer to the questions of rights that arise when a patient or nonpatient source supplies biological materials to an academic or commercial researcher. Because neither judicial precedents nor statutes directly address this question, the court must do what common law judges have done for centuries: reason by analogy, using legal principles and precedent developed for other circumstances.

Three large collections of legal principles could prove relevant to the use of human tissues and cells: property law, tort law, and contract law. These three areas include a broad variety of statutes and precedents that might be relevant and thus this issue could arguably touch almost all facets of U.S. law (see table 2). **Overall, however, there is no discrete body of law that deals specifically with these human biological materials.** Because common law reacts to damages only after they have occurred, it does not anticipate possible interests that have not existed previously. In the area of the use of human tissues and cells, technology in fact has advanced beyond existing law. It is not possible to predict what principles and arguments of law might actually be used as cases of this sort come before the courts.

Table 2.—Possible Sources of Rights Relating to Human Biological Materials

- **Law of Patents**
- **Law of Cadavers and Autopsies**
  - Property rights in corpses
  - Emotional distress caused by wrongful acts toward cadavers
- **Law of Organ Transplantation**
  - Donation of organs for transplantation
  - Sale of organs for transplantation
- **Law of Blood and Semen Sales**
  - Sale of blood and semen
  - Product liability generally
  - Implied warranties under the Uniform Commercial Code
  - Specific performance under the Uniform Commercial Code
  - Blood as a product for tax law purposes
- **Law of Copyright**
- **Law of Trade Secrets**
- **Law of Conversion and Trespass to Chattel**
  - Property interest
  - Possession
  - Injury to plaintiff
  - Abandonment
  - Res Nullius
- **Law of Accession**
  - Cases involving crops
  - Specification

SOURCE: Office of Technology Assessment, 1987.

Can Human Biological Materials Be Sold Like Property?

No area of law clearly provides ownership rights with respect to human tissues and cells. Nor does any law prohibit the use or sale of human bodily substances by the living person who generates them or one who acquires them from such a person, except under certain circumstances unrelated to biotechnology research. **In the absence of clear legal restrictions, the sale of tissues and cells is generally permissible unless the circumstances surrounding the sale suggest a significant threat to individual or public health, or strong offense to public sensibility.** To date, neither deleterious health effects nor public moral outrage have occurred even though occasional reports of sales of replenishing cells have been publicized. But while the law permits the sale of such replenishing cells as blood and semen, it does not endorse such transactions and does not characterize such transactions as involving property. In this sense, **either permitting or forbidding the sale of human specimens by patients and research subjects can be claimed to be consistent with existing law.**

INFORMED CONSENT AND DISCLOSURE

> Every human being of adult years and sound mind has a right to determine what shall be done with his own body . . .
>
> —*Scholendorff v. Society of New York Hospital,* 1914

The fundamental principle underlying the need for consent for medical or research purposes is respect for personal autonomy. Consent is a process of communication, a two-way flow of information between caregiver/researcher and patient/subject about the risks and benefits of the treatment or research.

For consent to be valid, the patient or research subject must be given an adequate amount of information with which to reach a reasoned choice. Although there are differences from State to State, the information that generally needs to be disclosed to obtain consent focuses on the nature and purpose of the treatment or research, risk-benefit information, and the availability of beneficial, alternative procedures or treatment. Consent in a research setting, like consent in a traditional treatment context, must be obtained in circumstances free from the prospect of coercion or undue influence.

There are two main sources of Federal regulations governing human research. The Department of Health and Human Services (DHHS) and the Food and Drug Administration (FDA) have promulgated regulations that delineate the elements necessary for informed consent to research. DHHS regulations govern research conducted or funded by DHHS, including the National Institutes of Health. FDA regulations govern clinical investigations that support applications for research or marketing permits for products such as drugs, food additives, medical devices, and biological products. Where these Federal regulations apply, disclosure requirements go beyond the accepted norms and include disclosure regarding confidentiality, compensation for research-related injuries, and the right to withdraw from research without incurring a penalty or loss of rights.

These Federal regulations are a deliberate attempt to set ethical and legal constraints on human research. A balance has been struck between the needs of researchers and the rights and safety of human subjects. The success of these regulations in achieving this balance is in no small measure a function of the integrity of investigators and the diligence of institutional review boards, which review proposed research projects for compliance with human subject research regulations.

Consent and the Prospect of Commercial Gain

The traditional view has been that in therapeutic settings, information disclosed to patients should be related to the risks and benefits of diagnostic tests or treatment, and that it should include alternative procedures. Similarly, in the research setting the disclosure of information has focused on the nature of the study and its effects on subjects. **Until recently, little thought had been given to disclosing information about the prospect for commercial gain, but with the advent of biotechnology and its potential use of human tissues and cells in valuable products, this issue merits consideration.**

Arguments can be made both for and against the idea of including information about potential financial gain in the required disclosure of information to patients and research subjects.

Arguments Favoring Disclosure of Potential Commercial Gain

If the notion of personal autonomy and the right to decide what will be done with one's body is to be given full legal recognition, then the prospect of commercial gain should be disclosed because this information may help a person decide whether or not to take part in research. Indeed, the overall trend has been toward greater disclosure of information—details about the probable impact of a procedure on lifestyle, the financial costs of one procedure over another, even the length of disability. Requiring disclosure about commercial gain can be viewed as a logical extension of the consent process.

In fact, it can be argued that the Federal regulations should explicitly require disclosure of potential commercial gain because they require disclosure of "significant new findings developed during the course of the research that may relate to the subject's willingness to continue participation." Discovery of a commercially significant tissue or cell in a subject's body may constitute a "significant new finding."

Arguments Against Disclosure of Potential Commercial Gain

The primary argument against disclosing the prospect of commercial gain concerns the impact such information might have on the subject's ability to reach an informed choice free of undue influence. The prospect of financial gain stemming from marketable discoveries could hamper subjects from reaching informed decisions because attention to this highly speculative topic could distract attention from other important aspects of the consent process.

Disclosing information about commercial gain could sometimes jeopardize the health and safety of subjects, as well as the validity of the research itself. The hope of gain, for example, might lead subjects to give less than candid answers to questions about medical or personal history that might otherwise disqualify them from the study. It might encourage them to expose themselves to risks they would otherwise consider unacceptable. In addition, because disclosure of potential gain is so speculative, such disclosure could generate unreasonable expectations or be considered misinformation.

It can also be argued that Federal human research regulations embody a philosophy that bans participation for inappropriate reasons. DHHS regulations, for example, make it clear that parole boards should not consider participation when making prisoners' parole decisions. DHHS might consider it improper for subjects to participate in research specifically because they might profit financially. Some people thus might argue that banning reference to the prospect of financial gain is necessary to safeguard subjects from undue influence on their decisions.

Are Changes Needed in the Consent Process?

The question of disclosing potential commercial gain related to diagnostic tests or treatment is one the courts or State legislatures will need to address. However, the Federal Government funds substantial amounts of human research and will also need to consider its regulations in light of this debate. **Policymakers, institutional review boards, and researchers face these questions related to disclosure: Should potential commercial gain be disclosed? If so, what pertinent information is necessary? When is such disclosure best made? What safeguards need to be developed to minimize any detrimental impacts resulting from disclosure of probable commercial gain?**

The prospect of financial gain is a troublesome issue in terms of voluntary consent and the use of human biological materials. **It can be argued that to assure truly voluntary consent, research subjects should not be offered compensation for their time and inconvenience, let alone substantial financial gain. The counter argument is that the sources of human tissues and cells have rights or interests in marketable substances taken or developed from their bodies and so have a right to know about potential profits or to be paid outright for their tissues and cells.** Regardless of what decision is reached, care must be taken so research is not adversely affected because it becomes too complicated to get specimens.

ECONOMIC CONSIDERATIONS

The traditional relationships between donors and researchers, and among researchers at different institutions, have been informal; both information and biological materials have been exchanged freely. Today, however, the techniques of biotechnology and the potential for profits and scientific recognition have introduced new concerns. At present, there is no widespread sentiment favoring a move toward a market system for the exchange of human tissues and cells. However, a few types of materials, such as plasma and some patented cell lines, are currently transferred within a market system. Future changes in the extent of profits generated from the biotechnology industry could force some changes in the current, primarily nonmarket system.

Two key factors probably will determine whether a change occurs in the current system of free donation of human biological materials for use in biotechnology research and commerce. First, a change could arise from judicial decisions in present or future cases under litigation. Second, a change could be initiated through greater public interest as the commercial applications of biotechnology increase and profits begin to be realized.

There are arguments both for and against payments for donations of human biological materials. Arguments over payments for human tissues and cells used in biotechnological research echo similar debates about markets in human organs. There are five principal issues in the debate:

- the equity of production and distribution,
- the added costs of payments to sources and costs associated with that process,
- social goals (the merits of an altruistic system of donations versus a market system),
- safety and quality (both of the source and the biological materials), and
- potential shortages or inefficiencies resulting from a nonmarket system or from changing from a nonmarket system to a market system.

The factors related to social goals, safety and quality, and shortages do not now offer compelling support either for or against paying the sources of human tissues and cells. But two of the issues are central to the debate, and they seem to argue in favor of opposing approaches. **Issues of equity argue in favor of a payment system to human sources. On the other hand, the added costs of payments to sources argue against such a payment system.**

Equity of Production and Distribution

The equity of a system can be considered from both the production and distribution sides. On the production side, one issue to consider is whether any of the participants are not receiving an equitable return for their services or products. On the distribution side, the main issue is whether there is adequate access to the goods by parties who seek them.

With respect to human biological materials obtained for research, **it can be argued that sources are not entitled to the value of their donated materials because they do nothing to develop the materials into the valuable product.** To a donor, replenishable tissue is often useless, and diseased tissue is actually a threat. It is only the intervention of the researcher that gives value to these materials. Therefore, it is the researcher who should legitimately realize any economic gains from cell lines or other products developed from the original biological material.

With respect to distribution, researchers generally cooperate with each other in supplying biological materials. The main incentive to this cooperation is the scientific commitment to the free flow of ideas and materials and to date the system has operated fairly efficiently. However, as biotechnological processes and products are commercialized, this free flow of information and materials is facing increasing constraints. **Shortages of human tissues and cells for basic research could occur if the incentives to cooperate are insufficient to motivate researchers to go to the trouble of supplying fellow researchers.**

Added Costs

Two types of additional costs would be incurred if human sources were compensated for their tissues and cells or if they shared in royalties accruing from licensing agreements concerning the transfer of developed cell lines: the actual compensation to the sources and the cost of administering the program (also called "transaction costs"). These costs could add significant burdens to the process of developing biotechnology products from human materials.

The actual compensation to the human sources of original tissues and cells is unlikely to have a large economic impact on the use of human biological materials, but transaction costs are likely to dwarf the costs of payments to these individuals. Studies involving the development of cell lines can take years to complete and commercial application years longer, so the cost of keeping records of the origin of all the cell lines involved might be considerable. In addition, most of the cell lines studied are unlikely to have any commercial value so a large portion of the transaction costs would actually be unnecessary. Furthermore, under a payment system scientists would no longer exchange materials freely; they would have to negotiate over the transfer and value of property rights for cell lines and might hesitate to share materials at all. Such negotiations would further increase transaction costs.

Resolving the Payment Dilemma

From the point of view of equity, a market structure is favored because it eliminates the potential windfall realized by those who would otherwise receive free tissues and cells. On the other hand, the magnitude of the transaction costs associated with payment to human sources may be sufficient to deter any forays into a market structure. Nonprofit organizations can play an important role in the procurement and distribution of human biological materials, just as they have played a key role in marketing blood and organs. **At present, there does not appear to be movement toward a change in the existing system of free donations of human biological materials for use in research and commerce in biotechnology.**

ETHICAL CONSIDERATIONS

Are the human body and its parts fit objects for commerce, things that may properly be bought and sold? **There are three broad ethical grounds for objecting to or supporting commercial activities in human biological materials: respect for persons, concern for beneficence, and concern for justice.**

First, the ethical principle of respect for persons relates to the idea that trade in human tissues and cells ought to be limited if the body is considered part of the basic dignity of human beings. To the extent that the body is indivisible from that which makes up personhood, the same respect is due the body as is due persons. If the body is incidental to the essence of personhood, however, then trade in the body is not protected by the ethical principle of respect for persons.

The second ethical principle relevant to the acceptability of trade in human materials is beneficence—who would benefit. The basic question could be stated this way: would commercialization of human materials be more beneficial than a ban on such commercialization? Marketing human tissues and cells might be justified if that would lead to only good results or to a preponderance of good results over bad. Those who hold differing ethical perspectives might consider different outcomes as beneficent.

A third relevant principle is justice. Would a market setting be equitable to all members of society, including those who are financially disadvantaged? Part of the public ambivalence about a market in human tissues stems from a sense that such a market would foster inequities.

The Moral Status of Bodies and Their Parts

Ethical and religious traditions do not provide clear guidelines about the ways in which human biological materials should be developed or exchanged. The absence of established customs regarding these materials is due to the relatively new potential for conducting and profiting from the development of human cells into cell lines. **The debate about whether or not it is ethical for bodily materials to be bought and sold underlies all discussions about the commercialization of human biological materials.** In addition, there are important questions about how justice

Box B.—A Hypothetical Case Study: How the Relationship Between Doctor and Patient Might Change

The possible commercialization of human tissues and cells raises significant new questions about the proper transfer and use of human materials and how such transfers will affect the relationship between doctor and patient.

Ms. Doe, a 42-year-old female, visits her gynecologist once a year for a routine pelvic exam, Pap smear, and mammography. In recent years, her physician's premiums for malpractice insurance have soared. Ms. Doe suspects that this is one of the reasons why she must now sign a sheaf of consent forms and waivers concerning the possible use of her tissues and cells, the possible hazards of exposure to radiation, and a host of other topics. She has come to regard her relationship with her doctor as one in which she is both vulnerable and unprotected. She is determined not to be completely outsmarted and has purposely not waived her rights to any commercial interest that may result from the use of her cells or developed cell lines.

Dr. Ray is a 50-year-old obstetrician-gynecologist beset with the problems and conflicts associated with conducting what had once been a satisfying practice in the modern technological world. She has been sued three times in the course of her 25 years of practice and in each case the charges have been dropped. Nonetheless, these experiences have caused her considerable stress and some humiliation. She no longer derives the satisfaction that she once did in her relationships with patients because she can no longer practice in a trusting fashion. When she first began her practice, she believed that her obligations were to benefit her patients and, above all, to do no harm. In recent years, she has had to change her approach from telling her patients what she thinks they need to know to providing them with an abundance of information so that they can make autonomous choices as recipients of health care.

Advances in biotechnology offer both Ms. Doe and Dr. Ray some potential recompense for what they both view as modern encroachments on what had heretofore been a relatively unencumbered and trusting relationship. Both have heard that it is possible and occasionally profitable to patent cell lines developed from unique cervical cells and both now wonder if the yearly routine Pap smear could be an opportunity for financial gain.

It is not farfetched to consider the ways in which modern developments in biotechnology might transform the relationship between doctor and patient. It is now possible to obtain something of value in any medical procedure that involves collection of a patient's tissues or cells, although the actual probability of profit is minimal. This possibility seems to entail new obligations regarding informed consent. The nature of these obligations, however, is a subject of some debate.

SOURCE: Office of Technology Assessment, 1987.

should be preserved in the distribution of profits accruing from developed human biological materials.

Decisions about the commercialization of human biological materials depend in part on the ways in which human tissues are regarded or valued. Selected Western religious traditions offer some insights about the significance of the human body. **Although there are significant variations among them, Jewish, Catholic, and Protestant traditions generally favor the transfer of human biological materials as gifts.**

There are two main reasons why it is important to examine religious perspectives when the goal is to develop public policies in a pluralistic society. One reason is historical: many of the laws regarding bodies and their parts have been influenced by religious sources. A second reason is that religious traditions still shape the ethical values of many people and hence they influence whether some uses of bodily parts or materials will be viewed as ethically acceptable or unacceptable. A related reason is that religious organizations have to be considered when policymakers try to develop policies that are politically feasible.

Two major variables are present in these Western religious traditions that affect the use of human tissues and cells: the type of materials and the mode of transfer. The significance of different modes of transfer (or acquisition, if viewed from the viewpoint of the user) and different materials hinges on various ethical principles, such as:

- respect for persons;
- benefits to others;
- not harming others; and
- justice, or treating others fairly and distributing benefits and burdens equitably.

There is a distinction between ethically acceptable and ethically preferable policies and practices. Some modes of transfer and some uses may be ethically preferred—for example, tradition prefers explicit gifts and donations without necessarily excluding sales, abandonment, and appropriation in all cases. Western religious tradition prefers transfer methods that depend on voluntary, knowledgeable consent. Thus, preferred methods recognize some kind of property right by the original possessor of the biological materials.

Tomorrow's Choices

Choices about how to handle transfers of tissues and cells from patients and research subjects to doctors, teachers, and researchers are important ethical decisions in two respects. First, these choices will characterize how individuals regard the human body. If certain human parts are "dignified," then social traditions suggest that they may be given, but not sold. Second, like the choice of how to obtain blood for transfusions, the system that is chosen for obtaining human tissues and cells will convey a sense of the symbolic weight modern society places on the human body and the use of human biological materials in order to relieve suffering and enhance human health.

The dispute between those who believe that commercialization of the human body is justified and those who think it is not is in part an argument between people who accept a philosophical view that separates the body (a material, physiological being) from personhood, identity, or mind (an immaterial, rational being) and those who do not.

POLICY ISSUES AND OPTIONS FOR CONGRESSIONAL ACTION

Four policy issues related to the use of human tissues and cells in biotechnology were identified during the course of this study. The first concerns actions that Congress might take to regulate the commercialization of human tissues and cells. The second involves the adequacy of existing regulations covering commercialization of cell lines, gene probes, and other products developed from human biological materials. The third concerns the adequacy of existing regulations covering research with human subjects. The fourth centers on whether present practice is adequate to ensure that health care providers disclose their potential research and commercial interests in the care of a specific patient or group of patients.

Associated with each policy issue are several options for congressional action, ranging in each case from taking no specific steps to making major changes. Some of the options involve direct legislative action. Others are oriented to the actions of the executive branch but involve congressional oversight or direction. The order in which the options are presented should not imply their priority. Furthermore, the options are not, for the most part, mutually exclusive: adopting one does not necessarily disqualify others in the same category or within another category. A careful combination of options might produce the most desirable effects. In some cases, an option may suggest alterations in more than one aspect of using human tissues and cells in biotechnology. It is important to keep in mind that changes in one area have repercussions in others.

ISSUE 1: Should the commercialization of human tissues and cells be permitted by the Federal Government?

Option 1.1: Take no action.

Congress may conclude that at present, the largely nonmarket basis for the transfer of human tissues and cells is appropriate. If a commercial market in human biological materials should arise, the lack of Federal regulation might result in great variability in the amounts of money paid to the sources of the original tissues and cells. If no action is taken, it is unlikely that human patients or research subjects will be routinely compensated for their tissues or cells in the near future.

Option 1.2: Mandate that donors of human tissues and cells are compensated for their donations.

Some people argue that in the interest of equity, the sources of human tissues and cells should be compensated. Congress could decide that human biological materials have a monetary value, even in their unimproved state, and that the sources of these materials have a right to this value. The amount and form of such compensation could vary. Sources could be paid for their time and trouble or paid for the actual specimen. Payment for service as opposed to substance is now standard practice in the case of sperm donation. Researchers argue that compensation for human tissues and cells in their unimproved form is impractical because the vast majority of these materials will have no ultimate value. Economists argue that the transaction costs of such compensation would outweigh any payment for the original biological material. In addition, many parties are concerned that any payment to the sources of human tissues and cells, no matter how small, would be so inefficient and inconvenient as to stifle research efforts in general. Lastly, some ethicists worry that any trade or market in human tissues and cells unacceptably alters the meaning and value of the human body.

Option 1.3: Enact a statute modeled after the National Organ Transplant Act that prohibits the buying and selling of human tissues and cells.

Congress may conclude that at present, the existing situation in which human tissues and cells are largely either donated or abandoned for research purposes is satisfactory. If Congress concludes that any for-profit market in human tissues and cells should be stifled or avoided, it could prohibit the sale of these biological materials. Such a statute would prevent patients, research subjects, or other sources from making money from providing their tissues and cells. If Congress enacted a statute modeled after the National Organ Transplant Act in particular, there would be a consistent line of Federal reasoning concerning the transfer of human organs, tissues, and cells.

ISSUE 2: Should the commercialization of cell lines, gene probes, and other products developed from human tissues and cells be modified by the Federal Government?

Option 2.1: Take no action.

At present, cell lines, gene probes, and other products developed from human tissues and cells are exchanged informally among researchers as well as by means of a market system. For the most part, profits are accrued in the form of royalties paid by those who want access to the developed products. If Congress takes no action, the use of patented inventions based on human biological materials will continue to be restricted to those who engage in licensing agreements for access to the patented products.

Option 2.2: Amend current patent law so parties other than inventors (e.g., patients, research subjects, or the Federal Government) have protected interests and access to any commercial products developed from their tissues and cells.

Within the context of current patent law, the inventor has exclusive rights to patented material and this effectively bars access by the sources to their original biological material. Some argue, however, that the patients or research subjects, particularly if they suffer from a disease, should have access to or some say in the use of patented products derived from their tissues and cells. At present, licensing agreements for the use of these patented materials do not commonly stipulate any protected interest for the original source.

Option 2.3: Enact a statute protecting the rights of patients or research subjects to share in profits accruing from licensing agreements for the use of cell lines or gene probes developed from their original human biological material.

The profitable features of patented cell lines and gene probes are the royalties that accrue from licensing agreements for access to these products. Congress may conclude that it is fair and equitable for the original sources of human biological materials to share in the derived profits. Such profit sharing could be in addition to or instead of a flat fee for the original unimproved tissues and cells. Some researchers argue, however, that it is often impossible to identify the source of the original material as cell lines and gene probes are developed. Many laboratory transformations over a long period of time separate the original sample from the patented invention. If Congress enacts a statute ensuring that the sources of human tissues and cells share in the profits accruing from licensing agreements, then an extensive and costly system of recordkeeping will be necessary to establish the identity and whereabouts of the original sources.

Option 2.4: Mandate that any cell line be presumed to be in the public domain unless it has been formally registered at the time the tissue was extracted or placed into culture.

The presumption that cell lines are in the public domain would bar anyone from claiming property rights to these products. While this would not directly compensate the donor or source of the unimproved tissues and cells or the researcher, it might relieve any sense of exploitation that someone else has taken over that original property right. The patent and similar systems could still apply for further inventions made in developing applications of the cell line.

Option 2.5: Enact a statute prohibiting parties other than inventors from sharing in any reimbursement for, or any profits derived from, the use of products developed from human tissues and cells.

Under the present market system, only those who have patent law protection or enter into a contractual relationship (e.g., licensing agreement) realize commercial gain from developed tissues and cells. Congress may conclude that the sources should be barred from obtaining any reimbursement for products developed from their tissues and cells. Such action would affirm that commercialization of products developed through the use of human biological materials should be limited to the patent holder and licensees, and that patients and research subjects have no right to the value of their tissues and cells in their altered forms. While such an action might serve as an economic inducement for those who would obtain human tissues and cells for the purposes of developing new inventions, it is arguably contrary to current patent and contract law (which encourages commercial negotiation between willing parties) as well as the concept of a person's autonomy over the use of bodily materials.

ISSUE 3: Are guidelines on the Protection of Human Subjects (45 CFR Part 46) issued by the Department of Health and Human Services adequate for the use of human tissues and cells in biotechnology?

Option 3.1: Take no action.

If no action is taken by the Department of Health and Human Services to alter the guidelines on the Protection of Human Subjects, it will remain unnecessary for researchers to inform subjects about possible uses of pathological or diagnostic specimens. As a result, researchers can continue to use these materials as they choose without informing the patient (see option 3.2). In addition, if the guidelines are not altered, it will not be possible for subjects to specifically waive their interests in the uses of their tissues and cells when giving informed consent because of the existing ban on the use of exculpatory language (see option 3.4).

Option 3.2: Direct the Secretary of Health and Human Services to modify or remove the exemption regarding the collection or study of existing pathological or diagnostic specimens from the regulatory requirements (§46.101(b)(5)).

Current DHHS guidelines exempt research involving the collection or study of existing data, documents, or pathological or diagnostic specimens if these are publicly available or if the donor is otherwise unidentifiable. Researchers are therefore not obliged to disclose their research interests to sources of specimens when this exemption applies.

Congress could modify or remove this section of the regulations so that it becomes necessary for research subjects covered by this exemption to be informed about and have some say in the use of their tissues and cells. This option would assure that additional research subjects would be informed of the possible uses of biological specimens and related data and may be consistent with the general spirit of the guidelines to protect the interests of the research subject. Removal of the exemption, however, could restrict research on a wide variety of currently available data, documents, records, and pathological or diagnostic specimens when a researcher cannot: 1) determine the identity of the subject, and 2) assure that the subject provided an informed consent as required by the DHHS regulations. Modifying the exemption by removing only pathological specimens or diagnostic specimens could likewise curb research using currently available unidentified specimens, but would continue the exclusion for other existing data, documents, and records.

Option 3.3: Direct the Secretary of Health and Human Services to amend the general requirements for informed consent (§46.116) to include potential commercial gain as a basic element of informed consent.

Under the current DHHS regulations, certain information must be provided to each subject during the informed consent process. It could be decided to add a provision requiring that in seeking informed consent, a disclosure be made regarding the potential for commercial gain resulting from data, documents, records, or pathological or diagnostic specimens obtained during the research. Such a requirement could be codified as a basic element of informed consent that shall be provided to each subject (§46.116(a)), or as an additional element of informed consent to be provided to each subject when appropriate (§46.116(b)). Such a requirement would make clear that potential commercial gain is an issue that would be reviewed by the Institutional Review Board.

Option 3.4: Direct the Secretary of Health and Human Services to remove the ban on exculpatory language as it pertains to commercial gain (§46.116).

Under the current DHHS regulations, informed consent documents may not include exculpatory language which is used to make research subjects or their representatives waive or appear to waive any of the subject's legal rights. The intent of this provision is to safeguard subjects and to make certain that they do not relinquish any legal rights. Some subjects may not want to reap financial benefits as the result of or as a byproduct of their participation in research, and some researchers and their sponsors may be deterred from conducting important research if they must share possible financial gain with research subjects. A change in the regulations could be made to modify the prohibition on the use of exculpatory language to permit research subjects to waive any rights to commercial gain. Such a provision would need to be clearly worded. Research subjects should understand exactly what rights are being waived and that they will not be denied treatment to which they are otherwise entitled even if they decide not to waive their rights. If the regulations are amended to permit the use of exculpatory language as it relates to potential commercial gain, the Institutional Review Board will have a greater role.

Option 3.5: Under its power to regulate interstate commerce, Congress could enact a statute to permit and regulate the buying and selling of human tissues and cells.

The advantage of such a statute is that it would offer the possibility of financial compensation to the sources of human tissues and cells. In addition, such a statute would apply to the interstate transfer of these materials from all sources and therefore go far beyond any alteration in guidelines for the protection of human subjects involved in federally funded research. The disadvantage of such a statute is that it would permit commercialization of all human tissues and cells transferred interstate and extend Federal regulation into a previously unregulated area.

ISSUE 4: Is present practice adequate to ensure that health care providers dis-

close their potential research and commercial interests in the care of a specific patient or group of patients?

Option 4.1: Take no action.

Congress may decide that existing or altered DHHS guidelines concerning the protection of human subjects provide sufficient safeguards to ensure that individuals are aware of the purposes and methods of the research in which they are involved. At the present time, however, these guidelines only extend to research subjects participating in federally funded research. There are no protections for research subjects in privately funded research.

There are no guidelines to ensure that health care providers disclose their commercial interests in caring for a particular patient or group of patients. If Congress takes no action, physician/researchers will not be obliged to tell a patient about their intention to develop commercially valuable products from the patient's tissues and cells. Congress may decide that the commercial interests of health care providers do not necessitate new forms of disclosure in order for patients to be adequately informed.

Option 4.2: Direct the Secretary of Health and Human Services to promulgate guidelines that require health care providers receiving any Federal reimbursement to disclose any research or commercial interests they may have in the care of a specific patient or group of patients.

If Congress acts to ensure that health care providers disclose their research and commercial interests in caring for particular patients, it will be necessary to discern what sort of commercial interests in particular merit disclosure. Physicians in private practice obviously have commercial interests in treating patients so their practice remains economically viable. It comes as a surprise to many people, however, to learn that their physician might also engage in research using a patient's tissues and cells and subsequently develop a profitable product based on these donated or abandoned materials. The relationship between physician and patient may be compromised if patients suspect that their caregivers may profit in unanticipated ways. The development of guidelines concerning this type of disclosure could promote greater trust between physicians and patients in the delivery of health care.

Chapter 2

Introduction

"I suspect at least the patient[s] should have some inherent right in the materials taken from them and any patents . . . at least for their lifetime and conceivably for their heirs' lifetimes."

—John Moore
Congressional testimony, Oct. 29, 1985

"I am lucky in that I am one of the so-called long-time survivors of [an acute leukemia research program]. If progress in the treatment of leukemia or anything else can be made through the use of my cells, then that is my contribution to mankind. I benefited from treatment which came about from years of scientific experiments, by many in and outside my particular place of treatment, funded by government grants as well as university, foundation, private and public funds."

"Human nature being such as it is, I would want to know of any breakthrough that came about as a result of my participation in research. But to those dedicated men and women in research belongs the glory. Without their endless quest, all would be for naught."

—Mildrene C. Thomasson
Washington Post, July 23, 1986

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Chapter 2

Introduction

> Experiment V. After evaporating two quarts of urine to dryness by gentle heat, there remained a white cake, which was granulated and broke easily between the fingers. It smelled like brown sugar, neither could it from the taste be distinguished from sugar.
>
> —Matthew Dobson, 1776

Although surely not the earliest use of a human biological material in research, this original observation concerning the urine of a diabetic patient was reported to the Medical Society of London in 1776 (12). Thus, the use of human materials in research is not a new issue. Over the past decade, however, technological advances have resulted in new, enhanced methods for studying and using human body parts—particularly tissues and cells. Using these technologies with intelligence, creativity, hard work, and a measure of serendipity, researchers have greatly increased our understanding of both human health and disease. Human samples are not only an integral part of the biomedical research process, but they are now also used as a component of (or in the production of) a variety of commercial products ranging from drugs and vaccines to pregnancy test kits.

Some of the new research and commercial uses of human biological materials have raised legal and ethical questions regarding the acquisition of bodily substances. These issues are novel; and little has been written about them. They are also extremely complex, and thus it is not surprising that there is no single body of law, policy, or ethics from which indisputable conclusions can be drawn. Questions to consider include:

- Are bodily substances "property," to be disposed of by any means one chooses, including donation or sale?
- Do property rights to genetic identity adhere to individuals or to the species?
- Who should make the basic decisions affecting the acquisition of tissues and cells, and under what circumstances should such acquisition be permitted or denied?
- What are patients and research subjects entitled to know about the potential for commercial exploitation of an invention that uses their bodily materials? And what is the probability that an individual's tissues and cells will end up in a commercial product?
- How is it that inventions incorporating human cells are patentable in the first place? How similar is the invention to the original biological material?
- What is the nature of the researcher's contribution versus the source's contribution to the invention?
- Who should profit from federally funded research using human tissue? To what extent are the issues raised by ownership of human biological materials related to the increasingly commercial relationships between universities and companies?

And, most importantly:

- What are the implications of these issues for scientists, physicians, patients, volunteer research subjects, universities, and the biomedical product industry?

This report does not address the use of tissue for the direct medical benefit of patients who need healthy human biological material—as is the case in organ transplantation, blood transfusion, or artificial insemination—except to the extent that similar legal, ethical, economic, and policy issues occur. Nor does this report explore the special concerns arising from research using special kinds of cells, such as fetal or germ cells.

DEFINITIONS

Biotechnology, broadly defined, includes any technique that uses living organisms (or parts of organisms) to make or modify products, to improve plants or animals, or to develop microorganisms for specific uses—including recently developed techniques such as gene cloning and cell fusion.

What are **human biological materials**? Human bodies contain a number of parts that can be useful in biomedical research. Healthy individuals continually produce a number of replenishable substances, including blood, skin, bone marrow, hair, urine, perspiration, saliva, milk, semen, and tears. Human bodies also contain nonreplenishing parts, such as oocytes or organs, which may either be vital (e.g., heart) or to some extent expendable (e.g., lymph nodes or a second kidney). Finally, diseased examples of these body parts also exist.

While OTA refers to all human parts—replenishing and nonreplenishing, living and nonliving, healthy and diseased—collectively as **human biological materials**, this report is primarily concerned with the biological materials that are most frequently obtained from humans and used in biotechnology: **tissues and cells**. The terms **specimens, samples, body parts, human tissue, bodily substances, primary tissue**, and **biologicals** are also used. **OTA distinguishes these undeveloped human biological materials from the biological inventions developed from them (and in some cases patented) such as cell lines, hybridomas, and cloned genes.**[1] These inventions, and the techniques investigators use to derive them, are described in chapter 3. The issue of patentability of most biological inventions in the United States is discussed in chapters 4 and 5.

CASE HISTORIES

Reports of sales of cells have generally aroused more public curiosity than controversy. In 1986, a Colorado company, Clonetics Corp., introduced the world's first commercial product that contains live normal cloned human skin cells (see figure 2-1). The product is sold to basic researchers who use it to study a variety of questions. Pharmaceutical, cosmetic, and other firms also use the cloned skin cells to test products. Clonetics uses samples from elective surgery (e.g., plastic surgery) that are purchased from both patients and doctors (3, 7,9).

In another instance, when hemophiliac Ted Slavin was discovered to have a high concentration of antibodies to the hepatitis B virus, he marketed his blood for up to $10 per milliliter (a milliliter is approximately ¼ teaspoon, so this is the equivalent of more than $6,000 per pint) to commercial organizations while providing it free to noncommercial hepatitis researchers. Slavin made news when he formed a company, Essential Biologicals, that not only marketed his own blood but that of others with rare blood characteristics. Before his death in 1984, his blood benefited research on the development of a hepatitis vaccine and prevention of liver cancer. Recently, clinical researchers who used Slavin's blood eulogized him as a gallant man who greatly contributed to biomedical research efforts (2).

However, disputes over the acquisition and ownership of human cells have occurred. While such cases have arisen infrequently, they have great practical significance to the parties involved and have been scrutinized by the research and corporate communities for their broader implications. Four cases involving human biological materials provide insight into the complex issues that can arise.

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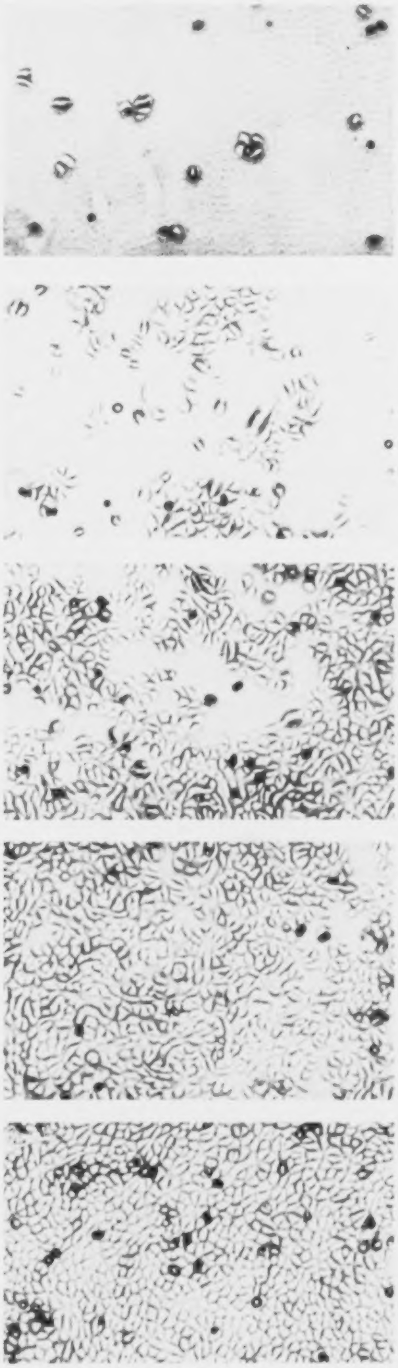
[1] "Products of nature," are unpatentable because they lack novelty (6). However, the biological inventions being patented today are not crude, unaltered products of nature. A claim to the entire genetic material of a single cell would probably be rejected; but one may properly seek a patent on an isolated gene encoding a protein of interest (see ch. 5).

Figure 2.—Normal Human Epidermal Cells in Culture



(A) 2 days after the skin samples are put into culture, clonal growth can be observed;

(B) after 4 days the colonies are developing rapidly;

(C) at 6 days the culture is ready to be shipped;

(D) after 8 days, the culture can be divided into two or more subcultures;

(E) 10 days after the first skin cells were seeded into culture, the human skin cells have multiplied to cover the surface of the growth chamber.

Normal human skin cells are supplied commercially in culture.

Photo credits: Clonetics Corp., Boulder, CO.

Case 1

In 1962, a Stanford University microbiologist working under a Federal research grant established the first strain of normal human cells in culture. After developing and cultivating the cell line, designated WI-38, the scientist formed a company to market the cells for use in the production of viral vaccines. The National Institutes of Health claimed that the cells were Federal property and charged him with wrongfully exploiting his federally funded research. Stanford was apparently about to take disciplinary action when the researcher resigned and filed suit seeking title to the cells. The dispute was finally settled out of court in 1981, with the scientist retaining the money from sales of the cells but with the question of ownership of the cell line still unresolved (11).

Case 2

In 1977, a man with leukemia agreed to allow a sample of his cells to be taken from his bone marrow for scientific research. Although the man died shortly afterwards, claims over who may profit from his cells continued.

Two research hematologists at the UCLA Medical Center (one of whom was also involved in case 2) succeeded in making the cells grow and divide, producing a new cell line that could be used to study leukemia. A sample of the new cell line, named KG-1, was sent to a National Cancer Institute (NCI) researcher with written instructions limiting its use. During a screening procedure, the NCI scientist noticed that the cell line produced a low concentration of interferon, a natural antiviral protein. The NCI researcher sent a sample of KG-1 to the Roche Institute of Molecular Biology, a wholly funded research arm of pharmaceutical manufacturer Hoffman-LaRoche, and they found that the cell line could be manipulated to optimally produce interferon. At Genentech, a biotechnology firm with contracts from Hoffman-LaRoche, techniques were used to isolate substantial quantities of the interferon gene from the cell line.

A dispute ensued between the University and Hoffman-LaRoche over who in fact owned the KG-1 cell line. The University, as home of the scientists who had developed the cell line, claimed ownership and the right to royalties from the production of interferon. Hoffman-LaRoche also claimed ownership and had even filed a patent application covering both the interferon and the manufacturing process. The dispute was finally settled out of court in 1983, with the drug company retaining the right to use the cells and genes in exchange for payment of an undisclosed sum to the University (11).

Case 3

In both the Stanford and UCLA cases, claims to cell line ownership were based on the intellectual (intangible) contributions of researchers. Legal conflict over cell line ownership has also occurred based on the tangible contribution of biological materials.

In early 1981, a researcher at the University of California, San Diego, was developing human hybridoma cell lines that would secrete antibodies to cancer cells. Learning of the project, Dr. Heideaki Hagiwara suggested the use of lymph cells from his mother, who was suffering from cervical cancer. The researcher agreed, and the Hagiwara cells were fused to an immortal cell line developed and patented by the investigator. A hybridoma that secreted an anti-tumor antibody was found.

Without the investigator's permission, Hagiwara took a subculture of the hybridoma cell line with him to Japan and gave it to the Hagiwara Institute of Health, directed by his father. The university and the Hagiwaras subsequently executed an agreement that permitted the Hagiwaras to use the cell line for scientific research but forbade their transfer to any other party for commercial purposes.

Several months later, the Hagiwaras asserted rights to the cell line and antibody, claiming that they had tangible property rights in the original tissue and were therefore entitled to a pecuniary interest in the derivative cell line. In 1983, the parties reached an agreement under which the university retained all patent rights and the Hagiwaras received an exclusive license to exploit the patent in Asia (4,13).

Case 4

In 1976, John Moore was diagnosed as having a rare form of cancer, hairy cell leukemia, a condition that affects an estimated 250 Americans each year (1). The recommended treatment for Moore's condition was removal of the spleen and surgery was performed at the University of California, Los Angeles Medical Center. As a patient, Moore had signed a standard surgical consent form (providing for the postoperative disposition of the tissue) to remove his diseased spleen, which had enlarged to approximately 40 times its normal size.

After the surgery, Moore's doctor and his technician developed a cell line (designated "Mo") from a sample of Moore's spleen obtained from the pathologist. These scientists found that the cell line developed from the spleen produced high quantities of a variety of interesting and potentially useful proteins. In 1979, the university applied for a patent on the "Mo" cell line and in 1984 a patent naming the scientists as inventors was obtained and assigned to the university. In 1981, the university, on behalf of the scientists, entered into a 4-year collaborative research program with two biotechnology and pharmaceutical companies for exclusive use of the "Mo" cell line.

After his splenectomy, blood samples were obtained from Moore by the doctor over the course of several years. In 1983, Moore initially signed a research consent form waiving any claims to the results of the university's research and giving the university all rights to products. On a research consent form signed at a later date, however, Moore refused to waive his rights to any products developed from his blood.

In 1984, Moore filed a lawsuit claiming that his blood cells were misappropriated, and that he was entitled to share in profits derived from commercial uses of these cells and any other products resulting from research on any of his biological materials (the patent for the "Mo" cell line clearly states that it was derived from splenic tissue). In March 1986, the trial judge dismissed Moore's complaint as failing to state a legally cognizable claim. As this report goes to press, this ruling is being appealed (5,8,10,14,15).

THE PROBLEM OF UNCERTAINTY

Uncertainty about how courts will resolve disputes between specimen sources and specimen users could be detrimental to both academic researchers and the infant biotechnology industry, particularly when the rights are asserted long after the specimen was obtained. The assertion of rights by sources would affect not only the researcher who obtained the original specimen, but perhaps other researchers as well.

Biological materials are routinely distributed to other researchers for experimental purposes, and scientists who obtain cell lines or other specimen-derived products, such as gene clones, from the original researcher could also be sued under certain legal theories (see ch. 5). Furthermore, the uncertainty could affect product developments as well as research. Since inventions containing human tissues and cells may be patented and licensed for commercial use, companies are unlikely to invest heavily in developing, manufacturing, or marketing a product when uncertainty about clear title exists.

Research using human biological materials could be thwarted if universities and companies have difficulty obtaining title insurance covering ownership of cells or genes, as well as liability insurance for related disputes. Insurance carriers will likely be concerned not only with suits by individuals who are identifiable as the specimen sources, but also by the potential for class action lawsuits on behalf of all those who contributed specimens to a particular research project. Researchers generally claim that the pervasive use of human tissues and cells in biomedical research makes it highly impractical and inefficient to identify the sources of the various specimens for purposes of valuing individual contributions. These concerns are addressed in chapter 7.

SUMMARY AND CONCLUSIONS

The government has always maintained an interest in the legal, ethical, and economic implications of research it is funding, and this interest is magnified when such research results in inventions that are patentable under Federal law. This report considers each of these aspects, as they apply to research and product development using human biological materials—undeveloped tissues and cells. The report also examines the scientific techniques that serve as the foundation of the boom in biotechnology and the parties interested in the boom.

This report does not address the use of tissues for the direct medical benefit of patients who need healthy human biological material—as is the case in organ transplantation, blood transfusion, or artificial insemination—except to the extent that similar legal, ethical, economic, and policy issues occur. Nor does this report explore the special concerns arising from research using special kinds of cells, such as fetal or germ cells.

Advances in technology and increased use of human biological materials for therapy, research, and commerce has raised a number of important questions that likely will need to be addressed in the immediate future. There are no easy answers. The issues are novel and complex and no single body of law, public policy, or ethics directly applies. But regardless of the merit of claims by the different interested parties, resolving the current uncertainty may be more important to the future of biotechnology than resolving it in any particular way.

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Chapter 3

The Technologies

"We must, as far as we can, isolate physiological occurrences outside the organism by means of experimental procedures. This isolation allows us to see and understand better the deepest associations of the phenomenon, so that their vital role may be followed later in the organism."

—Claude Bernard
1813-1878

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Chapter 3

The Technologies

Progress in the scientific techniques of biotechnology clearly has affected society on many levels—medical, social, economic, legal, and ethical. Most of the technologies used to transform undeveloped human tissues and cells mentioned in this report can be categorized into three broad areas: tissue and cell culture technology, hybridoma technology, and recombinant DNA technology. Advances in these technologies have increased our capability to identify and produce important human therapeutic agents. These fundamental scientific techniques are having profound, practical impacts on our society. Thus, it is important to understand the nature of the basic techniques and how they can be used to manipulate tissues and cells into useful products in order to appreciate the novel legal, economic, and ethical issues raised in this report.

The following brief review outlines the principal tenets of the three main techniques; the large-scale commercial applications of these technologies are discussed in another OTA report (23). While each technology is reviewed individually, keep in mind that it is the marriage of technologies that is the norm—no single technology is the central element in the development or commercialization of human biological material.

TISSUE AND CELL CULTURE TECHNOLOGY

Cells are the basic unit of all living organisms. They are the smallest components of plants and animals that are capable of carrying on all essential life processes. A single cell is a complex collection of molecules with many different activities all integrated to form a functional, self-assembling, self-regulating entity. Higher organisms and plants are multicellular, with certain cells performing specialized (i.e., differentiated) functions.

There are two broad classes of cells: prokaryotic and eukaryotic. The classes are basically defined by the manner in which the genetic material is housed. Prokaryotes, generally considered the simpler of the two classes, include bacteria. Their genetic material is not housed in a separate structure (called a nucleus), and the majority of prokaryotic organisms are unicellular. Eukaryotes, on the other hand, are usually multicellular organisms. They contain their genetic material within a nucleus, and have other specialized structures within their cell confines to coordinate different cellular functions. The genetic material of eukaryotic organisms is a structure called a chromosome—a DNA and protein complex that is usually visible to the eye with standard light microscopy. Humans are eukaryotes. Table 3 compares some of the features that distinguish microbial cells (prokaryotes) from cultured mammalian cells (eukaryotes).

Table 3.—Comparison of Microbial and Mammalian Cells

Characteristic	Microbial cells	Mammalian cells (in culture)
Size (diameter)	1 to 10 microns	10 to 100 microns
Metabolic regulation	Internal	Internal and hormonal
Nutritional spectrum	Wide range of substrates	Fastidious
Doubling time	Typically 0.4 to 2.0 hours	Typically 12 to 60 hours
Environment	Wide range of tolerance	Narrow range of tolerance

SOURCE: Office of Technology Assessment, 1987.

Multicellular eukaryotes are complex and difficult, if not impossible, to examine in vivo at the organismal level. Thus, scientists at the turn of the century began studying these organisms using a reductionist approach. They dissected the many biological processes in vitro by examining cells isolated and maintained independently of a whole organism. This approach, called tissue and cell culture, has been refined considerably over the years and the following section discusses this technology as it applies to human cells. A separate section is devoted to a special application of cell culture technology—making hybridomas.

Culturing Human Cells

The first experiments using tissue and cell culture technology were conducted in 1907 when a scientist successfully grew frog nerve cells in culture (7). The technology was originally considered a "model system"—a way for scientists to examine physiological events outside an intact organism. The approach was initially criticized as myopic and artifactual, but tissue and cell culture are now seen as fundamental scientific tools. These techniques are no longer only used as model systems, but are widely exploited techniques used in biomedical research.

As a practical matter, the distinction between tissue culture and cell culture is often blurred so the terms are frequently used interchangeably. Strictly speaking, in cell culture technology samples are removed from an organism and in vitro manipulation has destroyed the original integrity of the sample. In time, a sample isolated and established in the laboratory may be called a cell line. In tissue culture, isolated pieces of tissue are maintained with their various cell types arranged much as they existed in the whole organism and their functions remain largely intact. Tissue cultures presumably have more of their native identity, but are much more difficult to maintain than cell cultures.

Although many advances have occurred since 1907, establishing a human cell culture directly from human tissue—called a primary cell culture—is still a relatively difficult enterprise. The probability of establishing a cell line from a given sample is low. Success can be undermined by contamination during collection and storage, and is also dependent on how much damage the tissue suffered during collection of the sample. The success rate also depends on the type of human tissue being used. Some cells are easy to culture—human skin fibroblasts and human glial cells can be successfully established nearly 100 percent of the times attempted (14,19). Others, however can be very difficult to establish. Some human tumors can be cultured with about a 10 percent success rate (13).

While it is significantly less difficult to cultivate human cell lines than it is to establish them, working with human materials is still much more problematic than working with simpler organisms such as bacteria or yeast. Nevertheless, scientists are continuing to make progress in developing optimal growth conditions and cell culture equipment.

The food required to sustain human cells in culture is a liquid called growth medium. Different types of human cells require different growth media. Growth media are complex, and until recently animal serum—containing many unidentified, but vital components—was a necessary ingredient of all media. However, media with the identity and quantities of all components defined have been successful in sustaining long-term growth of human cells (8,20).

In addition to the many nutrient requirements of human cells in culture, strict temperature conditions must be maintained. Variation in temperature exceeding 2° C from the optimum usually is not tolerated; higher temperatures in particular are quickly lethal. Buffers are added to growth media to prevent drastic shifts in acidity, and the media must be sterilized. Contamination of samples during the early stages of culturing is a particular concern, and rigorous care must be taken to keep the culture free of contaminants such as yeast, fungi, bacteria, and viruses. Antibiotics and fungicides may be added to further discourage infestation. Table 4 lists some of the requirements for successful cultivation of human cells in the laboratory.

Table 4.—Some Nutrient and Growth Condition Requirements for Culturing Human Cells

Water
Salts
Sugars
Vitamins
Amino acids
Hormones
Fats
Buffers (to maintain proper pH—i.e., prevent drastic shifts in acidity)
Gases (oxygen, nitrogen, carbon dioxide)
Temperature (usually 98.6° F [37° C] for optimal growth)
Sterilization
Antibiotics and fungicides (optional)

SOURCE: Office of Technology Assessment, 1987.

Figure 3.—Plastic Monolayer Cell Culture Flasks

Photo credit: Ventrex Laboratories, Inc.

Cultured human cells grow as a suspension in solution, or attached to specially treated glass or plastic and submerged in growth medium (figure 3). Human cells typically double in number in 18 to 36 hours, compared to approximately 20 minutes for the bacterium *Escherichia coli*. Samples of human cells can be stored frozen in liquid nitrogen (−196° F) for future use. Certain types of cells are more fragile than others, but with modern freezing techniques most samples can be thawed and recovered decades later—often with a greater than 95 percent survivor rate.

Primary cell cultures are derived directly from solid human tissue or blood. In the case of cultures isolated from solid samples, extensive mincing or enzyme treatment may be necessary to disperse the tissue. **Since the earliest days of tissue and cell culture, it has been clear that not all the cells that are isolated from tissue and put into culture will survive. Thus, as soon as a sample is cultured it may not be representative of the total specimen used, and the longer the sample is in culture, the less it is like the original specimen** (2,4). For some liver cells, the fraction of cells resulting in viable outgrowth for any given sample is between only 1/1,000 to 1/100,000 (0.01 to 0.10 percent) (10).

Primary human cell cultures typically maintain the normal diploid number of human chromosomes—46. They may also exhibit the functions and properties indicative of their differentiated origin: liver cultures may produce certain liver-specific proteins or white blood cell cultures may express their own specialized characteristics.

Cell cultures isolated from nontumor tissue have a finite lifespan in vitro (i.e., most cultures die after a limited number of population doublings.) These cultures will almost always age unless pushed into immortality by outside intervention involving viruses or chemicals. This aging phenomenón, called senescence, does not occur en masse, but is a gradual deterioration and death of the cell population. The type of tissue involved and culture conditions are important variables in determining cell lifespan. However, the age of the human tissue source is also a component, and thus primary cell cultures can be studied as models of human aging.

Human Cell Lines

Long-term adaptation and growth of human tissues and cells in culture is difficult—often considered an art—but it has been accomplished and many established human cell lines (cells capable of continuous and indefinite growth in culture) exist. A primary culture that has been transformed into an immortal cell line usually has undergone a "crisis" period. Most established cell cultures have been derived from malignant tissue samples (figure 4). It is important to point out, however, that immortalization does not occur in all samples isolated from tumors. As was mentioned earlier, certain types of tumors seem more likely to establish continuous cultures. Figure 5 illustrates the evolution of cultured cells.

It is not known precisely why a given sample gives rise to a continuous cell culture. It is possible that a small number of cells in the original sample become the immortal cell line. On the other

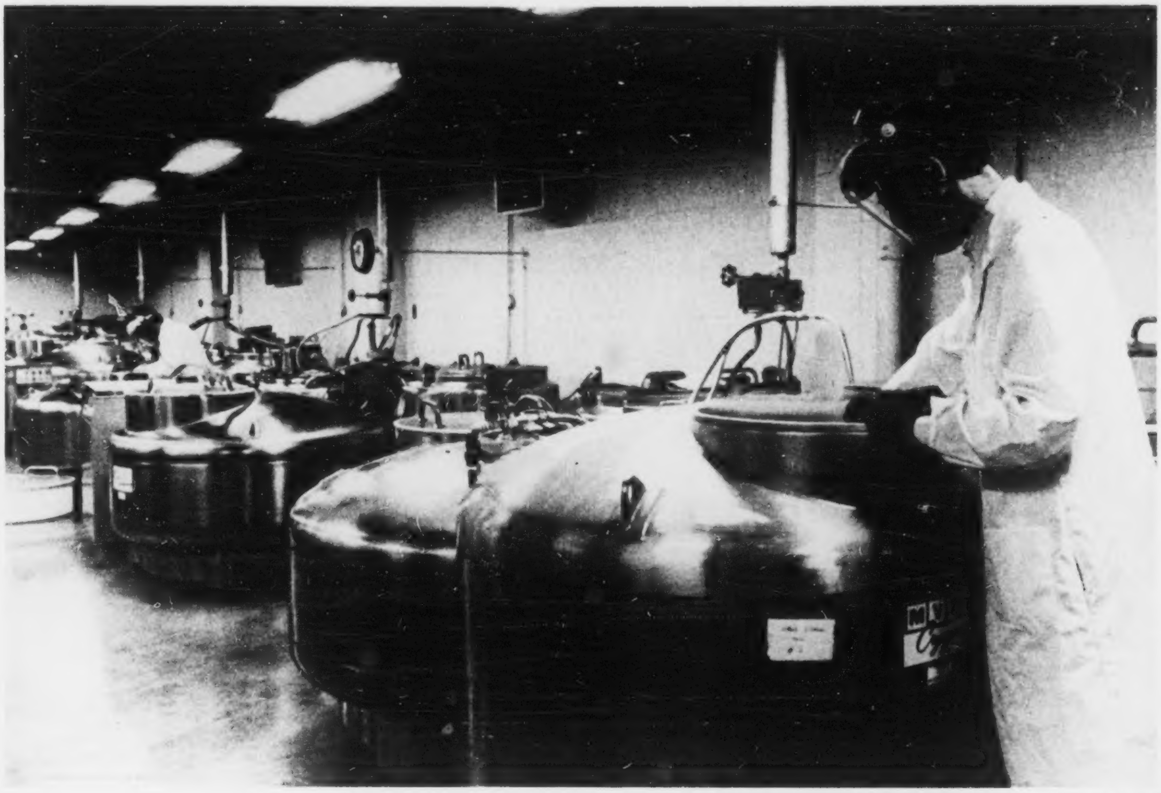


Photo credit: National Institutes of Health

Technician storing human cell lines in liquid nitrogen refrigerators.

hand, one or a few cells may undergo a transformation event during the "crisis" period to give rise to the immortal cell line. Evidence indicates that the latter explanation is more probable, but the possibility that there is a subpopulation of the original sample with a predisposition to undergo the transformation event cannot be discounted (4).

Established cell lines are usually aneuploid, which means that the number of chromosomes deviates from the normal number of 46 for humans. The first human tumor cell line, HeLa, was isolated in 1951 (5). Derived from a cervical carcinoma, this widely used cell line has a chromosome number that varies from about 50 to 80, depending on the particular isolate.

In addition to having aberrant numbers of chromosomes, established cell lines may not display differentiated functions. Both of these properties may be a result of the nature of the tumor used to establish the cell line, or they may be the result of changes the cells have undergone in order to achieve continuous, long-term culture. After initial immortalization, established lines are usually isolated and expanded from a single cell—a process referred to as cloning. This means that the entire population of cells has resulted after continual growth starting from a single cell.

Cells that have adapted to continuous culture can not be considered entirely representative of the total population of the original isolate and they may continue to change with time (4). Cloning is performed, therefore, to provide a uniform population of cells so that uniformity and accuracy in experimental results can be improved. But, continuous growth of cells is a dynamic process—subpopulations of cells may suddenly accelerate their growth rate, shut down production of or

Figure 4.—Human Tumor Cells in Culture

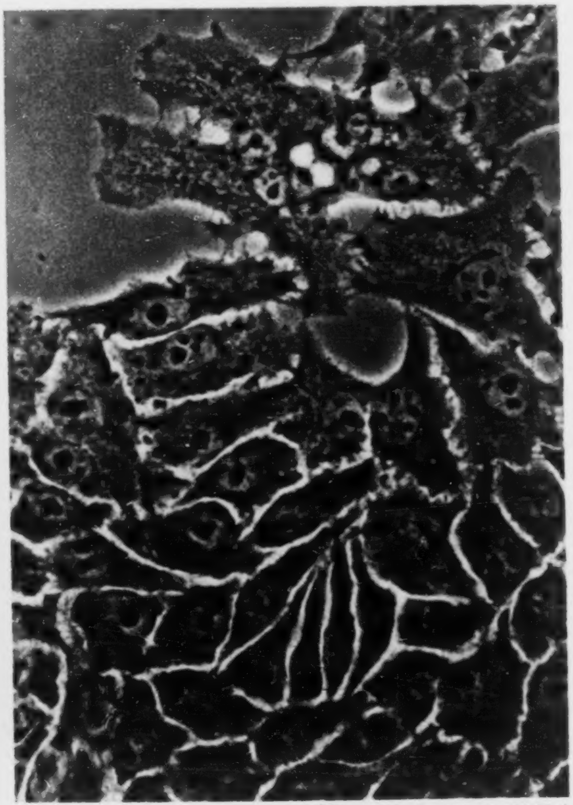


Photo credit: Robyn Nishimi

begin to overproduce compounds, or alter their chromosome number. So in order to reproduce earlier experimental results, repeated subcloning of cultured cells may be required.

Using Cell Cultures

The applications of tissue and cell culture technology are wide and varied. At both the basic research and commercial levels, cell cultures are used as tools to study basic biological processes. A cell line may be used as a biological factory to produce small or large quantities of a substance. Human proteins may be isolated directly from cultured cells. Cell cultures can also be the source of the genetic material needed to apply recombinant DNA technology in further studying a problem. As will be described later in this chapter, cultured human cells, both primary and established, play an important role in recombinant DNA technology. And finally, companies may use primary and established cultures to test drugs or the toxicity of compounds. The ability to maintain and manipulate many types of human cell lines in a controlled environment has expanded our knowledge of the biological sciences significantly and facilitated biomedical research.

In addition to increasing our knowledge, nearly 50 years after frog nerve cells were first cultured in vitro an important offshoot of growing cells in culture was invented: a technique to fuse cells from different sources. This technique, called cell fusion, has elucidated much of what is currently known about:

- the structure and function of the human genome,
- the expression and mechanism of heritable conditions,
- the regulation of normal biological reactions, and
- the processes of carcinogenesis and many other diseases.

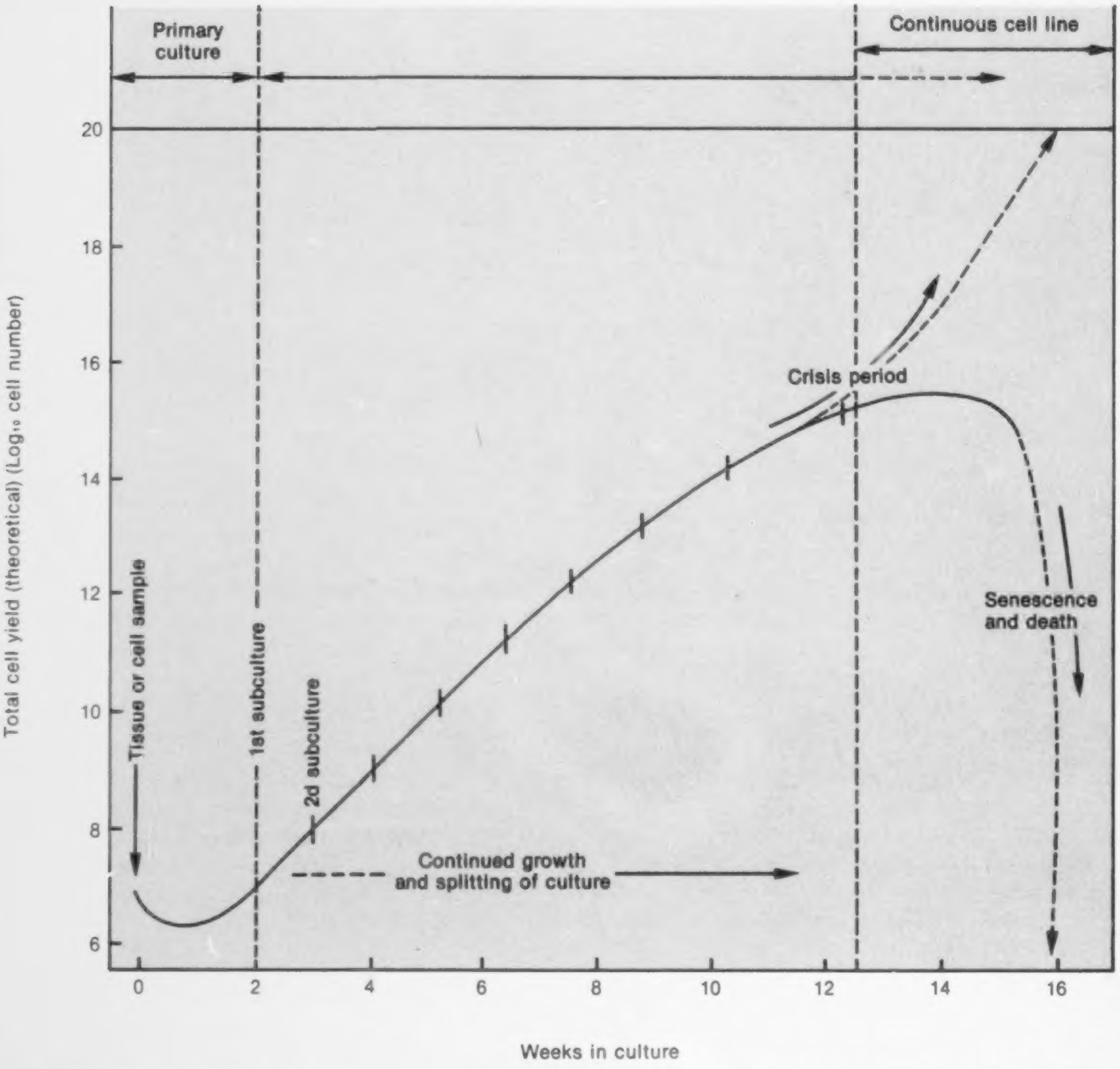
Cell fusion was also central to the development of hybridoma technology.

HYBRIDOMA TECHNOLOGY

Refinements in cell fusion (also called cell hybridization) are responsible for the explosion in hybridoma technology. Hybridomas are special types of hybrid cells and to understand how they were invented and why they are important it is helpful to understand the immune system.

The immune response in higher animals serves to protect the organism against invasion and persistence of foreign substances. It occurs only in vertebrates and is a cooperative effort among several types of cells that results in a complex series of events involving the production of antibodies

Figure 5.—Evolution of a Cell Line



The vertical axis represents total cell growth on a log scale and the horizontal axis the number of weeks the hypothetical sample has been in culture since it has been obtained from a donor. In this example, a continuous cell line is depicted as arising at about 12.5 weeks. Different cultures will give rise to a continuous cell line at different times. In addition, senescence may occur in a sample at any time, but for human diploid fibroblasts it usually happens between 30 and 60 population doublings (10 to 20 weeks).

SOURCE: Adapted from R.I. Freshney, *Culture of Animal Cells: A Manual of Basic Technique* (New York: Alan R. Liss, Inc., 1983).

and a class of molecules called lymphokines. Antibodies bind to a foreign invader, while lymphokines are necessary for coordinating, enhancing, and amplifying an immune response. Both antibody and lymphokine production operating in concert are necessary for a complete and efficacious response to a foreign challenge.

Scientists realized that obtaining a constant and uniform source of a single type of antibody would be essential to understanding the intricacies of the immune response and that such a uniform source of antibodies could provide a powerful, general analytical tool. High concentrations of reliable antibodies and lymphokines also promise rewards in diagnosing and treating human ills. The following two sections describe recently developed technologies that yield pure antibodies and higher concentrations of many lymphokines.

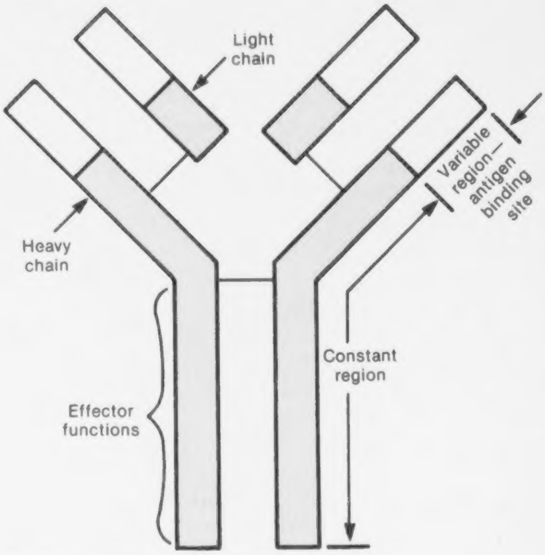
Monoclonal Antibodies

An antibody is a protein molecule with a unique structural organization that enables it to bind to a specific foreign substance, called an antigen. Antibody molecules have binding sites that are specific for and complementary to the structural features of the antigen that stimulated their formation. Antibodies formed by a sheep, for example, in response to injection of human hemoglobin (the antigen) will combine with human hemoglobin and not an unrelated protein such as human growth hormone.

All antibodies are comprised of four protein chains—two identical light chains and two identical heavy chains. These subunits are always linked in a fixed and precise orientation, as illustrated in figure 6. One end of the antibody contains two variable regions, the sites of the molecule that recognize and bind with the specific antigen. To accommodate the many antigens that exist, the variable end of an antibody differs greatly from molecule to molecule. The other end of the antibody is nearly identical among all structures and is known as the constant, or effector, region. The constant region is not responsible for antibody binding specificity, but has other functions.

Other important actors in the immune response are specialized white blood cells called lymphocytes that are present in the spleen, lymph nodes, and blood. A particular subclass of lymphocytes, called B lymphocytes or B cells, recognizes antigens as foreign substances and responds by producing antibodies highly specific for a given antigen. Any single B lymphocyte is capable of recognizing and responding to only one antigen. Once a B cell has been activated by an antigen it is committed to producing antibodies that bind to only that one specific antigen.

Figure 6.—Structure of an Antibody Molecule



SOURCE: Office of Technology Assessment, 1984.

During an immune response to an invasion by a foreign substance (e.g., a virus), one of the events that occurs within an organism is that many different B cells react and produce antibodies. Different B cells produce antibodies recognizing different parts (called determinants) of the virus, but as mentioned above, an individual B lymphocyte and its progeny produce only one specific kind of antibody. This multiple B cell reaction produces a mixed bag of antibodies with each type of antibody represented in only limited quantities, and is called a polyclonal response. Polyclonal antibodies can be isolated from blood serum, and, until recently, were the principle source of antibodies used by physicians and researchers. While antibodies produced this way were and still are useful tools to scientists and clinicians, a method to produce a constant and pure source of a single type of antibody was still sought.

The discovery in 1975 of the technique to produce a special hybrid cell known as a hybridoma that produces a specific type of antibody was, in the words of one of the inventors, a "lucky circumstance," but one with profound effects for biomedical research and commerce. Cesar Milstein and Georges Köhler,[1] working at the Medical Research Council's Laboratory of Molecular Biology in Cambridge, England, used the well-established tissue culture technique of cell fusion to produce a new type of hybrid cell—a hybridoma—capable of indefinitely proliferating and secreting large amounts of one specific antibody (11,12).

Hybridomas are hybrid cells resulting from the fusion of a type of tumor cell called a myeloma with a B lymphocyte freshly isolated from an organism (usually from the spleen or lymph nodes) that had been recently injected with the foreign substance of interest. Due to the recent exposure to the antigen, many of the B cells in such an organism will be producing antibodies specifically complementary to the foreign substance just injected. This enrichment process is a key step in hybridoma technology, since a human, for instance, is capable of producing up to a million different kinds of antibodies.

The hybridoma that results from the fusion of these two types of cells has characteristics of both cells. As is often the case with tumor cells, the myeloma parent cell has the ability to grow and multiply continuously in culture—it contributes this characteristic of "immortality" to the hybridoma. From the B cell, which is incapable of sustained growth and cultivation in vitro, comes the ability to secrete a single, specific type of antibody. Thus, a particular hybridoma clone is a distinct cell line capable of continuously producing one and only one kind of antibody—hence the name monoclonal antibody. The culture conditions and techniques used for hybridomas essentially are those described for tissue and cell culture.

Independently isolated lines of hybridomas, each originating from a single B cell fusing with a single myeloma cell, produce distinctive monoclonal antibodies. Each line is unique to the original contribution of the particular B cell parent. In the case of Milstein and Köhler each different hybridoma cell line isolated is an immortal antibody-producing factory targeted toward a different part of a sheep red blood cell. The method used to produce mouse monoclonal antibodies is illustrated in figure 7.

Virtually all of the monoclonal antibodies currently being used in humans as therapeutic agents or imaging tools are rodent antibodies because the production of human hybridomas has been much more difficult than the production of rodent hybridomas. To avoid some of the complications in patients treated with rodent antibodies, refinements in human monoclonal antibody technology will be necessary. Researchers have developed ingenious in vitro methods and successfully isolated suitable immortal parental cell lines, so production of human hybridomas is rapidly progressing (16,17). Recently, researchers have developed a promising new method to produce large quantities of human monoclonal antibodies (1).

The availability of large supplies of monoclonal antibodies is revolutionizing basic research, medicine, and commerce. Researchers have come to value monoclonal antibodies as important tools for dissecting the molecular structure and mechanisms of genes; more often than not, monoclonal antibody technology is combined with recombinant DNA technology. High-volume production of rodent monoclonal antibodies has had a significant impact on the diagnostic industry in particular. Monoclonal antibodies are reagents that are easily standardized and provide reproducible results. These substances have been adapted to clinical and home test kits, such as pregnancy diagnostic kits, with much success. Use of monoclonal antibodies for prophylactic or therapeutic regimens in humans is in an embryonic stage.

Lymphokines

Two other specialized cell types involved in the immune response are T lymphocytes and macrophages. Like B lymphocytes, both of these cell

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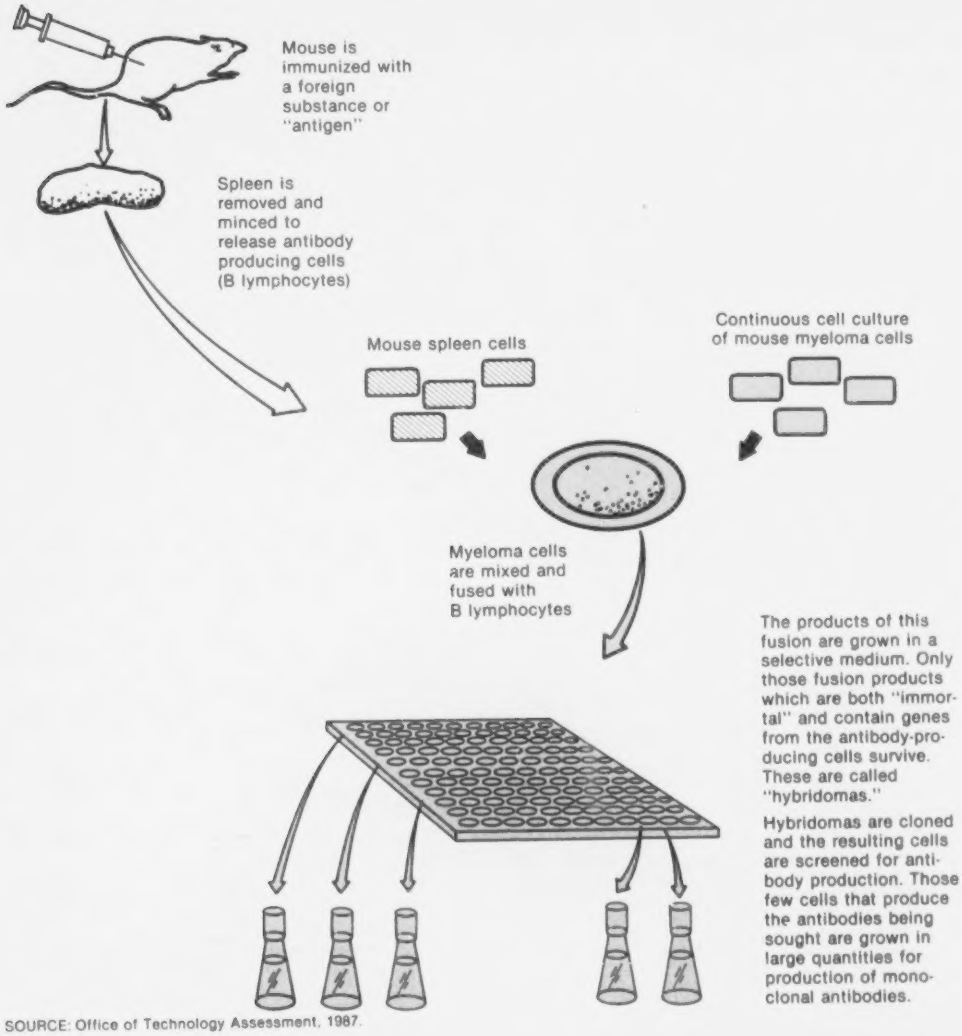
[1] In this case, the antibody recognized a particular part of a sheep red blood cell. It is interesting to note that Milstein and Köhler did not apply for a patent on this technique.

Figure 7.—Preparation of Mouse Hybridomas and Monoclonal Antibodies



Mouse is immunized with a foreign substance or "antigen"

Spleen is removed and minced to release antibody producing cells (B lymphocytes)

Myeloma cells are mixed and fused with B lymphocytes

The products of this fusion are grown in a selective medium. Only those fusion products which are both "immortal" and contain genes from the antibody-producing cells survive. These are called "hybridomas."

Hybridomas are cloned and the resulting cells are screened for antibody production. Those few cells that produce the antibodies being sought are grown in large quantities for production of monoclonal antibodies.

SOURCE: Office of Technology Assessment, 1987.

types can detect and respond to the presence of foreign substances. However, rather than producing antibodies, T cells and macrophages produce a variety of protein molecules that regulate the immune response. These molecules serve as messengers that transmit signals between cells to orchestrate a complete and efficient immune response against a foreign invader. The term "lymphokines" was coined in 1969 to describe this group of nonantibody immune response modulators (3). Since that time, more than 90 lymphokine activities have been described.

Lymphokines may recruit other cells to participate in and augment an immune response. Some lymphokines stimulate B cells to produce antibodies. Other molecules are released that suppress the immune reaction or ensure that the system focuses on the irritant and does not run rampant in a nonspecific attack that would damage host tissue.

Lymphokines are present in human blood in extremely small amounts—on the order of parts per billion. Interferon, for example, has been the most widely examined lymphokine to date by virtue of its relatively "high" abundance. It takes approximately 65,000 liters of blood to produce 100 milligrams of interferon (21). A comparable task would be the search for less than one-eighth of a teaspoon of salt in a swimming pool. Thus, scientists knew that to use lymphokines to treat human illness would require a source yielding a high-quality, high-quantity sample.

In addition to the problem of obtaining sufficient quantities of these important biological regulators, different lymphokines with antagonistic functions are often difficult to separate. In the past, such impure preparations of lymphokines have hampered efforts to understand the basic mechanism of how the immune system responds to cancer or an agent of disease. Autoimmune diseases, for instance, are aberrations of the immune system resulting in an organism attacking itself as a foreign substance. The availability of a lymphokine drug to suppress an individual's immune response could alleviate much suffering. Similarly, other lymphokines could be used as therapeutic agents to boost a patient's own immune system to combat a foreign invasion.

Recent progress in obtaining pure lymphokine preparations is a result of advances in cell culture, hybridoma, and recombinant DNA technology. Scientists have now developed cell culture conditions capable of sustaining continuous growth of cell lines producing elevated levels of one or more lymphokines. Some of these lymphokine-producing cell lines are derived from tumor cells that have been adapted to tissue culture conditions. Other cell lines have been isolated from normal cells that have been manipulated in a manner to transform them into immortal lymphokine-producing cultures.

The explosion in hybridoma technology also has influenced the study and development of hybrid T cell lines to produce lymphokines (6). Investigators have had some success producing these hybrid lymphokine factories, often referred to as T cell hybridomas. T cell hybridomas are the products of fusion events between immortal cancer cells and isolated T lymphocytes.

Even though researchers have isolated and identified many types of human cells producing lymphokines, these cell lines are still not capable of generating sufficient quantities of these molecules for widespread use. The human cell lines are very important, however, as rich deposits of source material to clone lymphokine genes. Several different genes have been cloned from human cells that produce measurable amounts of lymphokines (16), and once a particular lymphokine gene has been cloned, large quantities of the protein molecule can be obtained via the methods developed for large-scale production of recombinant DNA products.

Large-scale production of pure lymphokines now enables scientists to examine many aspects of the immune system puzzle by manipulating cells and lymphokines in vitro. The availability of commercial quantities of these pure immune regulators also affords physicians an opportunity to use lymphokines for treating human disease. Human alpha-interferon has been approved by the Food and Drug Administration (FDA) to treat certain medical conditions and interleukin-2 is being used in clinical trials to combat certain types of cancers or viral infections. Table 5 lists some of the lymphokines that have been characterized and have received considerable attention for their possible use as human therapeutic agents.

Table 5.—Some Lymphokines With Therapeutic Potential

Interferons
Interleukin-1 (also known as lymphocyte activation factor)
Interleukin-2 (also known as T cell growth factor)
Interleukin-3
Interleukin-4
Colony stimulating factors
B-cell growth factor
Macrophage activity factor
T-cell replacing factor
Migration inhibition factor

SOURCE: Adapted from A. Mizrahi, "Biologicals From Animal Cells in Culture," *Bio/Technology* 4:123-127, 1986.

RECOMBINANT DNA TECHNOLOGY

History

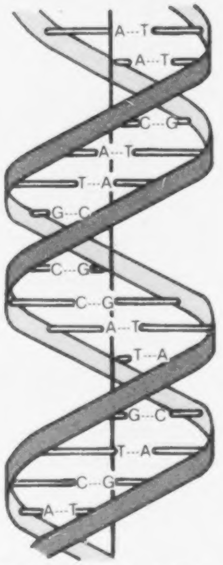
In 1865, Mendel postulated that discrete biological units were responsible for maintaining characteristics in organisms from one generation to the next. The faithful transmission, or inheritance, of these units—called genes—is common to the entire spectrum of living organisms. It is a result of the remarkable capacity of a living cell to encode, translate, and reproduce a chemical into its ultimate biological fate. The chemical responsible for inherited characteristics is deoxyribonucleic acid, or DNA.

In 1965, a century after Mendel described the concept and principles of inheritance, also called genetics, the term "genetic engineering" was coined (9). The term genetic engineering is now also popularly referred to as "gene cloning" or "recombinant DNA." These techniques usually involve direct manipulation of the genetic material—the DNA—of a cell. Rather than rely on the appearance of spontaneous mutants or laborious extraction of minute quantities of a valuable substance from tissue, it is now possible to use these techniques to isolate, examine, and develop a wide range of biological compounds quickly. Like the use of cell culture, the use of recombinant DNA techniques is a reductionist approach that has shed further light on the molecular details of regulation of many important biological processes, including arthritis, cancer, and development. The principal advantages of these techniques are speed and ease of application.

Gene Cloning

DNA, which takes the structural form of a double-stranded helix (figure 8), is the information system of living organisms. DNA in all organisms is composed, in part, of four chemical subunits called bases. These four bases—guanine (G), adenine (A), thymine (T), and cytosine (C)—are the coding units of genetic information. These bases normally pair predictably—A with G, and T with C—to form the DNA double helix structure. It is the unique ordering of these bases in the helix that determines the function of a given gene, and the complete blueprint for an organism is coded within its DNA.

Figure 8.—The Structure of DNA



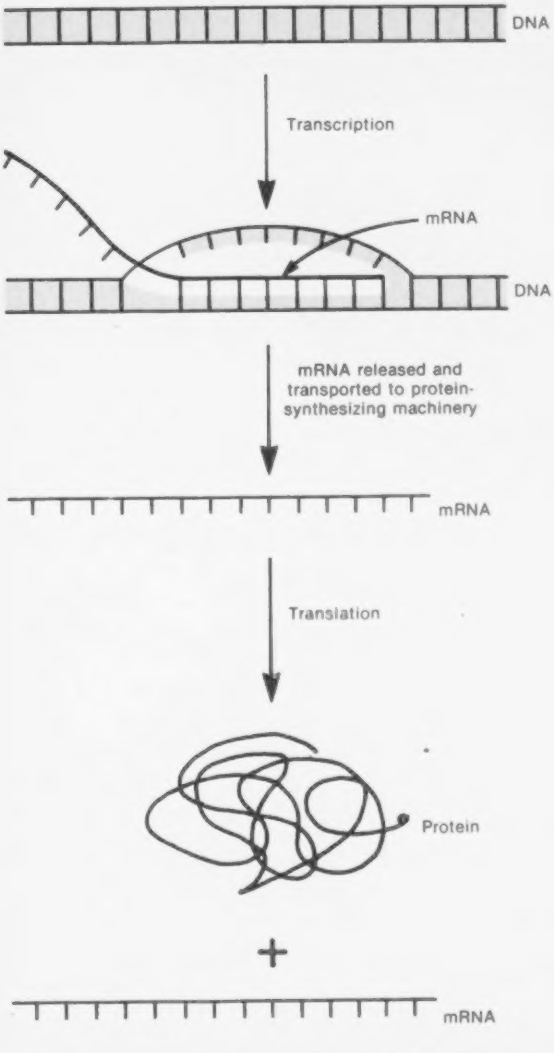
SOURCE: Office of Technology Assessment, 1984.

There are two broad categories of genes: structural and regulatory. Structural genes code for products, such as enzymes—proteins that catalyze biological reactions. Regulatory genes function like traffic signals, directing when or how much of a substance is produced. The process whereby the code of DNA is interpreted and a protein synthesized is summarized in figure 9.

All cells, except egg and sperm cells and some cells of the immune system, contain the total information capacity of the organism. Thus, the DNA present in one human cell is identical to all other cells within the individual and has the capability of directing all possible functions. In individual human cells, however, not all functions operate simultaneously.

The amount of DNA present in each cell of a human being is 3.3 billion base pairs (15). About 50,000 genes make up the complete human master plan, and the average gene contains about 1,000

Figure 9.—The Process of Gene Expression


DNA
Transcription
mRNA
DNA
mRNA released and transported to protein-synthesizing machinery
mRNA
Translation
Protein
+
mRNA

During gene expression, the genetic material of an organism is decoded and processed into the final gene product (usually a protein). In the first step, called transcription, the DNA double helix unwinds in the area near the gene, and a product called messenger ribonucleic acid (mRNA) is synthesized. This piece of mRNA is a single-stranded, linear sequence of nucleotide bases chemically very similar to DNA and it is complementary to the section of the unzipped DNA. The second step of the process is called translation. The mRNA is released from the DNA, becomes associated with the protein-synthesizing machinery of the cell, and is decoded and "translated" into a protein product.

SOURCE: Office of Technology Assessment, 1987.

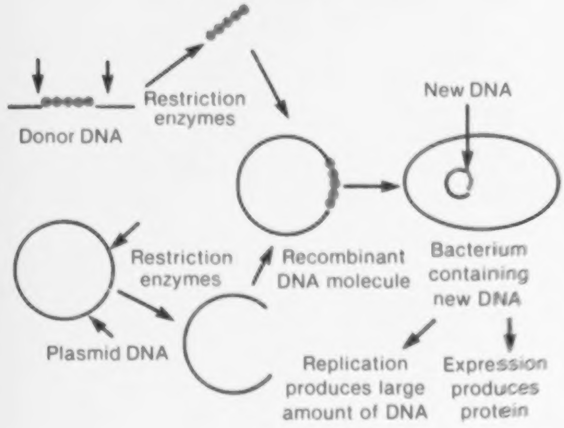
base pairs. Since this accounts for about only 50 million base pairs, it is apparent that not all of the DNA within a human cell is devoted to modulating or specifying a particular gene product. To date, specific functions have only been assigned to about 50 million of the 3.3 billion base pairs present in humans. There is speculation that some of the unassigned 3.25 billion base pairs may contain some genes, but that much of the "excess" DNA is for architectural or other unknown functions.

Gene cloning refers to a process that uses a variety of procedures to produce multiple copies of a particular piece of DNA. Since the amount of DNA in a human cell is enormous compared to the amount present in an individual gene, the search for any single gene within a cell is like searching for a needle in a haystack. Therefore, a range of tools have been developed that allow investigators to both identify a gene and amplify the number of copies of the gene. As a metal detector allows easier detection of a needle in a haystack, and a photocopy machine reproduces documents, "recombinant DNA technology" is a group of methods that accelerates the investigation or production of genes. The specific details of these methods to join segments of DNA—sometimes from different species—vary from project to project and purpose to purpose. In general, however, all recombinant DNA methods require the following:

- a suitable vector,
- an appropriate host,
- a system to select host cells that have received recombinant DNA, and
- a probe to detect the particular recombinant organism of interest.

Perhaps the hallmark discovery that allowed scientists to clone genes was the isolation of naturally occurring enzymes in bacteria that recognize and cut DNA at specific strings of bases. The string of bases recognized by the enzyme is usually four to six bases in length and depends on the particular bacteria from which the enzyme is isolated. These enzymes, called restriction endonucleases, are used in gene cloning to fragment DNA into discrete, precise segments. Recent reports have described modified restriction en-

Figure 10.—Recombinant DNA: The Technique of Recombining Genes From One Species With Those From Another


Donor DNA
Restriction enzymes
New DNA
Restriction enzymes
Recombinant DNA molecule
Bacterium containing new DNA
Plasmid DNA
Replication produces large amount of DNA
Expression produces protein

Restriction enzymes recognize sequences along the DNA and can chemically cut the DNA at those sites. This makes it possible to remove selected genes from donor DNA molecules to form the recombinant DNA. The recombinant molecule can then be inserted into a host organism and large amounts of the cloned gene, the protein that is coded for by the DNA, or both, can be produced.

SOURCE: Office of Technology Assessment, 1987.

zymes that are now capable of cutting DNA at a sequence of the investigator's choice (18,22). With the aid of restriction enzymes, a particular fragment of DNA—often the gene of interest and some neighboring bases—can be excised away from large, unwieldy pieces of DNA.

Cloning human and other eukaryotic genes is usually more difficult technically than cloning bacterial and viral genes. Refinements in recombinant DNA methods, however, have been invented. Figure 10 illustrates the basic technique for preparing a recombinant DNA molecule. The recombinant molecule can be prepared in a number of ways, but ultimately the process involves linking the DNA sequence of interest to a second piece of DNA known as the vector.

Vectors serve as vehicles for the isolation and high copy reproduction of a particular DNA fragment free from its normal environs. Vectors can be bacterial, viral, phage, or eukaryotic DNA—or they may be combinations of these DNAs. The characteristics of vectors differ from construction to construction. Some are capable of stably maintaining a large piece of foreign DNA, some reproduce rapidly and in high copy number, while others, called shuttle vectors, can reproduce and function in both eukaryotic and prokaryotic cells. A critical consideration in commercial development of a cloned gene is the ability of the vector to achieve high product expression.

The other principal player in a cloning system is the host organism. Once foreign, or donor, DNA has been inserted into the vector, the recombinant molecules must be introduced into an organism that provides an optimal environment for increasing the number of copies of the cloned DNA, producing large amounts of a gene product, or both. The host is often the bacterium *Escherichia coli*, but human cells, yeasts, and other cells can be suitable hosts. Mean generation time, ease of culture, ability to stabilize and adjust to presence of the vector(s), and ability to add sugar groups to a gene product are some important factors to consider in selecting a host.

In general, recombinant DNA technology works in this sequence: first, donor DNA is cut by restriction enzymes into many fragments, one of which contains the sequence of interest. These different fragments are joined with vector DNA to become recombinant DNA molecules. The recombinant molecules are then introduced into the host; for a variety of reasons, only some host cells will take up the recombinant DNA. After this process, the fraction of host cells that received any recombinant DNA must be identified. This initial selection is often accomplished through the use of antibiotics that kill those host cells that did not receive recombinant molecules.

Finally, the small number of recombinant organisms containing the specific donor DNA fragment of interest must be found. This process is completed via a tool that detects the gene or gene product of interest. This tool is called a gene probe. Examples of gene probes include a segment of DNA similar to the gene of interest, but from a different organism; a synthetic fragment of DNA deduced from the protein sequence of a gene product; a piece of RNA; or an antibody that binds to the product of interest.

Once identification and purification of the genetically engineered (recombinant) organism has been achieved, the host population containing the cloned gene can be expanded and the cloned gene used to identify, isolate, and scrutinize scarce biological compounds.

SUMMARY AND CONCLUSIONS

Technologies grouped under the umbrella term "biotechnology" include tissue and cell culture, hybridoma technology, and recombinant DNA technology. Tissue and cell culture, the oldest of the three technologies, involves converting undeveloped human biological materials into cell lines capable of indefinite growth in a laboratory. Establishing human cultures is still a relatively difficult enterprise, and the human cell line resulting from any single sample has undergone many changes. Continuous cultivation of cell cultures requires stringent control of temperature, nutrient, pH, and sterile conditions. The use of human cell lines in research has contributed much to our knowledge about human genetics and the regulation of normal and abnormal biological processes. Cell lines also have been used for a broad range of commercial purposes.

Hybridoma technology is a spinoff technique from cell culture. Hybridomas are special hybrid cells that are produced by fusing two types of cells: an antibody-producing B lymphocyte and a tumor cell called a myeloma. A hybridoma is capable of multiplying continuously in culture (a property it receives from the myeloma) as well as secreting antibodies with a single specificity (an ability gained from the B lymphocyte). The antibodies produced by hybridomas are called monoclonal antibodies. Not only are monoclonal antibodies important laboratory tools, but some are significant commercial commodities. One specific mouse monoclonal antibody was approved by the FDA in 1986 for use in the treatment of kidney transplant rejection.

Lymphokines are molecules that are secreted by specialized cells called T lymphocytes and macrophages. Many of these substances occur naturally in the human body, but were previously available in minute and usually impure amounts—if at all. Lymphokines, also called bioregulators or biological response modifiers, have significant therapeutic promise in the treatment of a spectrum of diseases because of their exquisite specificity and reduced toxicity. Hybridoma, cell culture, and recombinant DNA technologies permit lymphokines to be isolated in pure form and in quantities facilitating further analysis or use. Human alpha interferon, a lymphokine produced by a combination of the biotechniques, was approved in 1986 by the FDA for use in the treatment of one form of leukemia.

Genes are composed of DNA and they are responsible for the faithful inheritance of characteristics from one generation to the next. Recombinant DNA technology, also called genetic engineering, involves techniques that allow direct manipulation of the genes—the DNA—of a cell.

DNA? IS THAT A GOVERNMENT AGENCY?

Courtesy of: L. Gonich and M. Wheelis, The Cartoon Guide to Genetics

Gene cloning uses a variety of these recombinant DNA techniques to join segments of DNA, sometimes from different species, in a form that allows multiple copies to be made. These multiple copies can then be used to examine the regulation of a biological process, identify and isolate scarce compounds, or produce commercial quantities of an important substance. Three commercial products created through gene cloning—human growth hormone, human insulin, and human alpha interferon—have been approved for use in humans by the FDA.

The ease of application of biotechnology processes has allowed researchers to turn undeveloped human tissues and cells into human biological products with significant therapeutic promise and commercial potential. Yet the ultimate value of these technologies may not be simply their end products; their greater value may be the insights they provide about disease processes.

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Chapter 4

The Interested Parties

> "Biomedical research is in considerable measure so esoteric an activity that a great deal of the social control that guides it must be in the hands of the biomedical research community itself. Yet, like all other specialized and esoteric social activities, biomedical research is too important to the larger society to be left entirely to its experts. In part it needs to be effectively and continuously scrutinized and controlled by outsiders. An effective system of control, including both insiders and outsiders would better protect all the parties of interest . . ."
>
> —Leon R. Kass
> *Science*, 174:779-788, 1971

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Chapter 4

The Interested Parties

Why has controversy arisen over the use of human biological materials, and who are the stakeholders in this controversy? How has it even come to pass that naturally occurring substances, such as genes, plasmids, and even organisms, can be patented? While the technological advances described in chapter 3 have increased the availability and promise of new inventions and products of great importance to human health, the changing legal climate in the United States also has been a factor responsible for increasing interest in human biological materials. These events have led to an increased commercial interest in human specimens and have affected three major groups of stakeholders: the sources of human tissues and cells, the research community, and the biotechnology industry.

WHY COMMERCIAL INTEREST IN HUMAN BIOLOGICAL RESEARCH AND INVENTIONS?

The controversy that has arisen over the use of human tissues and cells can be attributed in part to two landmark events that occurred in 1980 to accelerate industry-sponsored research and interest in human biological materials. First, the U.S. Supreme Court held for the first time that Federal patent law applies to new life forms created by DNA recombinations, thus opening the possibility that products containing human cells and genes might also be patentable. Second, Congress amended the patent statute to encourage patenting and licensing of inventions resulting from government-sponsored research.

Patentability of Recombinant and Nonrecombinant Cell Lines

In the early 1970s, General Electric microbiologist Ananda Chakrabarty used both classical genetic selection and recombinant DNA techniques to find and develop a novel bacterial strain capable of digesting oil slicks. Chakrabarty and his employer sought patent protection under the Federal patent statute (35 U.S.C. 101). While judging the process for producing and maintaining the new bacterium to be patentable, the Patent and Trademark Office examiner rejected patent claims to the bacterium itself. The Patent and Trademark Office's Board of Appeals upheld the examiner's rejection on the ground that living organisms were *per se* unpatentable.

Later, the U.S. Court of Customs and Patent Appeals (CCPA) reversed this ruling (29), relying on a prior decision in *In re Bergy* that held "the fact that micro-organisms are alive is a distinction without legal significance" (27). *Bergy* concerned the creation of a biologically pure culture of a naturally occurring but previously undiscovered micro-organism capable of efficiently producing an antibiotic similar to penicillin. A patent had not been sought for the naturally occurring micro-organism, but one was sought for the purified sample and the processes used to create the pure culture.

A chain of related Supreme Court and CCPA decisions ultimately led to a five-to-four Supreme Court ruling upholding the CCPA's decision that genetically engineered micro-organisms are within the scope of patentable subject matter defined by section 101. The high court's *Diamond* v. *Chakrabarty* decision (14) makes it clear that **the question of whether or not an invention embraces living matter is irrelevant to the issue of patentability, as long as the invention is the result of human intervention.**

The court did not directly address the question of whether purified nonrecombinant cell samples are patentable since *Chakrabarty* dealt with a genetically recombined organism and the *Bergy* case was not directly considered. However, the CCPA's second *Bergy* decision (28) suggests that a purified strain of naturally occurring organisms is statutory subject matter unless precluded under the "product of nature" doctrine (6).

Under the product of nature doctrine, a cell or other substance occurring in nature is not patentable unless it is given a substantially new form, quality, or property not present in the original (6,46). Purification of a naturally occurring substance or organism must result in a substantial change in its characteristics, functions, or activity for the purified material or cell line to be patentable (6). If a patent examiner decides to reject patentability for an invention on grounds that it is a product of nature, he must show that the claimed product, such as a biologically pure culture, is **likely** to exist in nature as a result of natural processes and not merely that it **possibly** exists in nature (6,56).

The Patent and Trademark Office has historically taken the position that, in the absence of a Supreme Court ruling addressing the issue, higher life forms such as mammals, fish, and insects will not be considered to be patentable subject matter under section 101 (56). This position finds some support in a statement in *Bergy* that biologically pure cultures created and used for their chemical reactions are more similar to inanimate chemical compositions than they are to animals or plants (27). However, the rationale for this position is somewhat weakened by the Court's statement in *Chakrabarty* that "Congress intended statutory subject matter to include anything under the sun that is made by man" (14).

Patenting and Licensing of Government-Sponsored Inventions

The Federal Government is the primary source of funding for basic biomedical research. Yet until 1980, no single patent policy existed with respect to government-supported research. Each agency developed its own rules, resulting in 25 different patent policies, and under this system, only about 4 percent of some 30,000 government-owned patents were licensed (40). Furthermore, the government policy of granting nonexclusive licenses discouraged investment, since a company lacking an exclusive license was reluctant to pay the cost of developing a product and building a production facility. Potentially valuable research thus remained unexploited.

Congressional concern about this so-called "innovation lag" prompted efforts to develop a uniform patent policy that would encourage cooperative relationships between universities and industry, with the goal of taking government-sponsored inventions off the shelf and into the marketplace. In 1980, Congress passed the Patent and Trademark Amendment Act (Public Law 96-517) and added additional amendments in 1984 (Public Law 98-620).[1] The law allows nonprofit institutions (including universities) to apply for patents on federally funded inventions, with the Federal agency retaining a nonexclusive worldwide license. Universities are required to share royalties with the inventor and to use their own share for research, development, and education. The patent policy of the National Institutes of Health (NIH) served as a model for the uniform patent policy established by the law.

Effect of 1980 Patent Law Changes on Biocommerce

The impacts of technological breakthroughs and the changing legal climate on human biological product development is demonstrated by a 1985 survey of American medical institutions conducted by the House Science and Technology Committee's Investigations and Oversight Subcommittee. During the 5 years from 1980 to 1984, patent applications by universities and hospitals for inventions containing human biologicals increased more than 300 percent as compared with the preceding 5-year period and constituted 22 percent of all patent applications filed by these institutions. Forty-nine percent of all medical institutions have applied for such patents (50).

Whether these and forthcoming patents will be of commercial value is difficult to assess. The pharmaceutical industry has usually experienced a higher rate of commercial value for its patents than industry in general (10). There is reason to believe that biopharmaceuticals will have a still higher rate since they often have the potential to supplant an entire, well-established market occupied by a conventional drug (41). At this point, however, it is still too early to determine what pattern will be established in the biotechnology industry for the commercial value of patents.

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[1] The U.S. Department of Commerce recently requested comment on revised regulations under this statute (51 FR 22508).

SOURCES OF HUMAN TISSUE

Individuals who are sources of human tissues and cells are one major group of people affected by the U.S. Supreme Court and congressional actions contributing to increased development and commercialization of human biological materials. Tissues and cells can be removed from sources for medical purposes, research purposes, or both. The primary medical reasons for withdrawing human biological materials are diagnosis (removal of specimens to determine the nature and extent of a disease) and therapy (removal of diseased tissue, either permanently or for treatment and reintroduction, as in renal dialysis or homologous bone marrow transplants). Removing human specimens can involve a variety of procedures, including:

- aspiration of bodily fluids (e.g., blood, amniotic fluid) through a needle;
- examination of cells from a surface (e.g., skin or cervix cells from a Pap smear);
- surgical removal of nonsurface tissue (e.g., lymph node biopsy, tumor material); and
- noninvasive procedures to collect excretions (e.g., urine and feces) and certain secretions (e.g., semen, saliva, milk, and perspiration).

There are three major categories of sources of human tissues and cells: patients, healthy research subjects, and cadavers.

- Patients are a source of both normal and atypical specimens and these individuals may or may not be research subjects. Patient-derived specimens may be "leftovers" from diagnostic or therapeutic procedures and most human tissues or cells that find their way into research protocols are of this type. Patient-derived samples can also be provided as part of a research protocol.
- Healthy volunteer research subjects may donate replenishing biologicals if specimen removal involves little or no risk of harm, according to generally accepted principles of human subject research.
- Cadavers are the only permissible source of normal and atypical vital organs (including the brain, heart, and liver, but excluding kidneys and corneas). They are also the only permissible source of healthy organs (e.g., corneas) destined for research rather than transplantation.

While the different classifications of human sources—patient, volunteer research subject, or cadaver—may seem to be fairly straightforward, the human relationships involved between sources and physician/researchers (or another interested party) are more dynamic than these categories suggest.

For example, the distinction between an individual as a patient versus a research subject can sometimes change over the course of time. The relationship between physician and patient can also evolve from physician-patient to researcher-subject. Thus, if a patient's specimen is removed for diagnostic or therapeutic purposes and the physician subsequently uses the specimen in research, should the patient still be considered a patient, or has he become a research subject and has the relationship become one between research subject and researcher? Or, if a patient hospitalized with a broken leg is asked to donate a blood sample, should he be considered a research subject because any risk he undergoes is for altruistic rather than selfish reasons, or is he still a patient because of the possibility that he may feel coerced to cooperate with the hospital staff on whom he is physically and psychologically dependent?

Determining whether a person is a patient or a research subject is relevant in determining the applicability of Federal regulations governing federally funded research using human biological materials. These issues are addressed further in chapter 6.

THE RESEARCH COMMUNITY

Investigators who use human tissues and cells in their research are a second stakeholder in the controversy about access, use, and profit from specimens. A recent survey conducted by the House Committee on Science and Technology found that 49 percent of the researchers at medical institutions surveyed used human tissues or cells in their research (50). According to one recent estimate, at least 500 principal investigators nationwide use human cell lines (42). NIH provides grants to about 200 individuals whose primary research focuses on human cell lines and to an undetermined number of scientists whose secondary interest is human-related (34). The use of human specimens is principally due to three factors:

- the newly emerging abilities to isolate increasingly smaller amounts of important naturally occurring human biological factors (also known as biopharmaceuticals, bioresponse modulators, or biological mediators);
- the ability to produce virtually unlimited quantities of these factors, usually found in minute amounts in the body, through recombinant DNA methods; and
- the invention of hybridomas, making possible the generation of large, pure supplies of specific antibodies (47).

Obtaining Human Biological Materials for Research

Although tens of thousands of samples of human tissue are probably used in research, detailed information on the amount and type of human biological materials used is difficult to obtain. No central records are kept on this data, and information on the source or use of human biologicals by biotechnology companies is often considered confidential business information. Moreover, the ways in which researchers obtain human samples vary with the type of scientist and the nature of the research.

Physicians working at a university hospital will often obtain tissue as a result of biopsies or surgery done on their patients. The physician/researcher may obtain samples directly from the operating room in cases when fresh, live tissue is needed, or receive the material after pathologists have examined it (48).

Nonphysician researchers or clinicians needing human tissues or cells that are not obtainable from their own patients or patients within the hospital obtain specimens by other avenues. Informal transfers are common among researchers at hospitals and universities around the country. Researchers and companies are becoming more cautious, however, and are moving toward a much tighter, more formal system of transferring research materials. This caution is a result of concerns over patent and ownership rights and it applies to newly isolated tissue, as well as investigator-developed cell lines and gene clones (41,43).

Researchers at some large universities and research institutes also can obtain needed material from volunteers who are asked to donate tissue samples. For example, at NIH, blood is collected by the NIH Blood Bank specifically for research purposes. Most volunteer donors are members of the NIH staff, although some outside donors are also used. Payment for blood donations for research purposes is usually about $25. Volunteers providing bone marrow for research purposes receive around $75 for a specimen (45). Generally, these types of arrangements are ad hoc, and no systematic data are available on the amounts and type of human materials collected or on payments for such material.

Researchers at biotechnology and pharmaceutical companies who need human biologicals also have a variety of options at hand for obtaining materials. They can pay individual volunteers for occasional specimens, usually of blood, or purchase outdated blood from the Red Cross or other blood banks. Biotechnology companies often obtain specimens as a result of their research relationships with universities and medical research centers. The biotechnology company may obtain specimens either through individual affiliations with university/hospital researchers or through research arrangements with university and hospital departments (12,25,38,41,43).

Organized repositories provide an additional avenue for both noncommercial and commercial investigators to obtain research material. Most of the material available from these "warehouses" are not human biologicals as defined in this report—i.e., primary tissues or cells—but are cell lines or gene clones (containing human DNA pieces) developed and discovered by investigators and deposited at the repositories. Organizations in this field are usually funded by NIH and operated on a nonprofit basis, providing samples of tissue and genetic material to qualified researchers for a nominal processing fee. Many universities and cancer research centers maintain their own collections as well. Table 6 lists some of these facilities and indicates some of the types of material each stores.

Although no systematic survey was undertaken for this analysis, anecdotal information suggests that most university or other nonprofit researchers usually are able to obtain the samples they need for research, but individuals who need certain types of tissue must make their own arrangements. The process, however, of obtaining samples is sometimes characterized as a "scramble." Additionally, odd samples are usually less in demand than some common types of cancer or tissue. Research popularity coupled with a higher incidence of a particular tumor can result in fierce competition for a continued supply of new specimens. Colon and bladder carcinomas are two tissues currently in high demand (1,13,23).

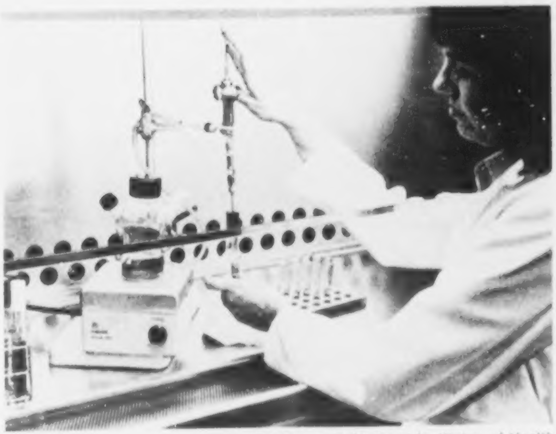


Photo credit: National Institutes of Health

Human cell lines at the American Type Culture Collection's Human Tumor Cell Bank are put into ampules for shipment to researchers.

Table 6.—Repositories for Human Tissues and Cells, Cell Cultures, and Cloned Genes

Organization	Type of material collected
The American Type Culture Collection (ATCC)[a]	Cell cultures, cloned genes
The Human Genetic Mutant Cell Repository,[b] Coriell Institute (formerly the Institute for Medical Research)	Cell cultures
The National Cancer Institute, Biological Carcinogenesis Branch	Sera, tumor tissue (benign and malignant)
The Cell Culture Center, Massachusetts Institute of Technology	Cell cultures

[a] The ATCC is one of the largest repositories of its type, maintaining some 40,000 cultures, including about 1,325 human cell lines (48). These materials are provided to nonprofit researchers for an average fee of $40 and to for-profit researchers at an average fee of $64. Many researchers send samples of their cell cultures to the ATCC (or other repositories) once they have been developed and reported to avoid the time and money required to respond to requests for samples from other researchers. Samples are required to be placed in a repository if a patent application has been filed relating to the sample. Access to samples for which patents are pending is strictly restricted; once a patent is granted, the sample is available to anyone. In 1985, ATCC distributed between 12,000 and 19,000 human cell cultures to researchers, the majority of which went to universities and hospital research centers (see refs. 19,35).

[b] The Human Genetic Mutant Cell Repository, with 3,550 human cell lines in stock, responded to 3,472 requests in 1985 (see refs. 52,53).

SOURCE: Office of Technology Assessment, 1987.

To assist in this process, various organizations, networks, and interchanges, are undertaking more comprehensive coordinating activities. In 1980, a nonprofit organization, the National Disease Research Interchange (NDRI), pioneered the world's first retrieval/preservation/distribution mechanism for organs and tissues. NDRI makes over 100 types of tissues available to researchers studying a wide range of diseases, including diabetes, retinitis pigmentosa, cardiovascular disease, cystic fibrosis, and glaucoma (55). In response to inquiries, the National Cancer Institute (NCI) has issued a request for cooperative agreement applications to establish a cooperative network, including computer communication, to improve collection and distribution of human cancer tissues (54). The network is not a tissue bank, but will respond to requests from investigators to help them obtain the multiple fresh tumor samples they need to screen for tumor protein markers, genes, and other characteristics (1). NIH recently awarded a contract to the University of Minnesota Hospital in Minneapolis for a "Liver Tissue Procurement and Distribution System." This program is designed to establish regional centers to collect livers removed from transplant patients and then distribute them to researchers nationwide. Finally, a project at the University of Alabama is also being designed to address shortages in the availability of tissue for research (23).

Uses of Tissues and Cells in Research

The research community uses undeveloped tissues and cells provided by sources for a wide range of purposes. Material obtained from an individual is not necessarily used strictly for research purposes, however, but can be divided for medical, research, or commercial uses. In fact, diagnostic, therapeutic, research, and commercial uses of biologicals are usually intertwined, sometimes inextricably. The present economic dynamics of research coupled with the proliferation of biotechnology companies have spawned a plethora of university-industry relationships that have made it increasingly difficult to separate the use of human samples in university (or other institution-based) basic research from basic and applied research in commercial settings.

Uses of human tissues and cells in basic research are diverse and thus difficult to categorize. Once human biological material is provided by an individual, it is examined, manipulated, and developed by researchers. Human tissues and cells can be examined directly from the patient with limited handling (e.g., screened for a particular tumor marker) or they can be manipulated extensively to obtain a useful research tool or potentially marketable product. Generally, basic researchers use these materials to study the characteristics and functions of healthy and diseased organs, tissues, and cells.

The researcher's choice of a source of specimen is based on the type of tissue being studied and the goals of the particular research project. The material could be used for a "one-shot" experiment or used in the long-term development of something (e.g., a cell line, cloned gene, or gene probe) that expands the base of knowledge about a complex problem and advances the investigator's project. Specimens can also be used by the researcher to create cell lines that generate a continual supply of products such as monoclonal antibodies; provide insight into a patient's hereditary disease; provide the basic genetic material from which recombinant products can be produced; or serve as a medium to propagate viruses or amplify cloned DNA sequences. At the most fundamental scientific level, human material is used in experiments to examine and understand basic biological processes. This basic research can subsequently lead to other uses of human tissue, such as product development by the commercial sector.

Commercial enterprises use specimens as raw materials for both product-oriented purposes and nonproduct-oriented basic research. The use of human biologicals by companies for nonproduct research differs little from that just described for nonindustrial research. In product-oriented research, a specimen could be used for a one-time process to produce or test something, or it could be used as part of a long-term investigation to produce a product. Proteins might be extracted from human specimens or tissue culture cell lines derived from specimens. Similarly, genes for these useful proteins might be isolated by industrial researchers directly from undeveloped material or from an established cell line. These cloned genes can then be used to mass produce large quantities of therapeutic or diagnostic human-derived products. Human insulin, human growth hormone, and human alpha-interferon are three products produced through recombinant DNA techniques that are licensed for therapeutic use in the United States. Standardized diagnostic products (e.g., pregnancy test kits) often contain human proteins.

Companies also sometimes use human-derived material to study the efficacy of an item prior to marketing, to meet safety criteria, or to manufacture a biological product such as a viral vaccine. Specimens can be used as reagents in federally required, preclinical testing of pharmaceutical products (44). Use of such reagents is necessary to develop the potential value of the product, but is not itself the marketable item. The material used by the company for testing or manufacturing could be newly isolated specimens or standard cell lines. The new technologies, such as hybridoma technology or recombinant DNA technology, led the Food and Drug Administration (FDA) to recently amend its regulations to establish general requirements for cell lines used for manufacturing any biological product for human use (51 FR 44451).

Some firms maintain that they do not use any original human tissue in research, concentrating their efforts on established cell lines instead. These companies obtain and manipulate generally available cell lines, resulting in new, unique, or improved cell lines.

The Research Process and Rarity of Human Tissue

To what extent are human biological materials, provided by any single (or very few) individual(s), potentially profit-yielding to the research community because the material is both commercially useful and rare? Biomedical research and development using human material is a dynamic process that rarely culminates in a profit-making product. **Research results are typically a series of several joint efforts with specimens provided by several individuals.** This diversity is critical to advancing the knowledge about an area under study and the expectation of developing a commercial product at the outset of the research is often extraordinarily small. **Thus, any product developed is a consequence of many source and researcher contributions. A determination of the contribution of any single individual in the marketable product would be speculative.**

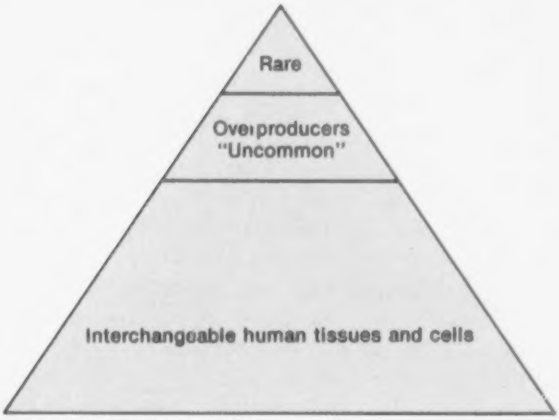
In general, the value to the researcher of certain types of tissue results more from the key issues of access and availability to the sample than from the inherent rarity or commercial potential of the tissue. Both industry and nonindustry-supported investigators usually are interested in a specified type of tissue that occurs with a known frequency in the population, but cannot be termed truly rare—such as cells from a cystic fibrosis patient; a particular type of tumor (e.g., breast, lung, liver, or other); or a collection of samples from several generations of a family. Certain types of specimens might be more easily obtained (e.g., blood instead of bone marrow), or certain samples might not be commonly removed during surgery (e.g., healthy spleens). The typical goal when obtaining human specimens is acquiring any liver tumor, for instance, not obtaining one from a specific individual that is truly rare.

Although the goal of a researcher is often to obtain many random samples of human tissue or cells, once a scientist has investigated different tissue samples it may become apparent that one or a few specimens (or the cell line the investigator has developed) "overproduces" an interesting substance. Some people might naturally produce greater than normal amounts of a substance, or some might overproduce it because of an illness. This overproduction could enable the researcher to identify a novel entity that would otherwise have gone undiscovered, or the overproduction could be useful in further research and experiments (21)—particularly if the investigator has been fortunate and able to establish a culture of the sample that continues the overproduction. Thus, once found (usually serendipitously) a novel tissue or cell can become a valuable research tool or be developed into a potential commercial product. It should be emphasized, however, that a systematic method of obtaining such unique tissues or cells does not appear to exist. **Furthermore, unique human samples do not necessarily have any actual or potential commercial value.**

It is conceivable, of course, that one person or only a handful of people are overproducers of a potential commercial substance. More likely, however, many people are overproducers but simply have not been identified by researchers (nor could they feasibly be identified). Furthermore, while some people are overproducers, nearly all persons are capable of being high, moderate, or low producers of the substance (unless an individual has a deletion in the gene for the substance—which is a rare condition itself), and once the substance has been identified with the aid of the overproducer, it usually can be detected in and isolated from anyone's tissue. Thus, while the original specimen(s) may have been useful to initially identify an interesting product, its value for commercial exploitation is diminished because the sample is not truly rare.

In a few instances, however, a specific biological substance is sought in a group of individuals to produce a specific quantity of a pharmaceutical product (which may or may not be produced with the aid of biotechnology). These sources are usually paid for their specimens; the amount paid depending on a variety of factors, including the

Figure 11.—Rarity of Human Tissues and Cells Used in Biotechnology



SOURCE: Office of Technology Assessment, 1987.

number of people who are potential sources. An example would be the bleeding of people with chronic hepatitis who have the viral antigen necessary to prepare hepatitis B vaccine from human serum (9). In these isolated instances, a reasonable attempt can be made to determine the ratio of source material to final commodity.

In summary, **the issue of rarity in human biologicals used in biotechnological research takes the form of a pyramid** (see figure 11). At the bottom are the vast majority of materials, relatively common and easy to obtain (though by no means does this imply an infinite supply). Much farther up the pyramid is an intermediate level, where particular samples may exhibit uncommon characteristics (e.g., the overproducers of certain substances mentioned above) or occur in the population at a low frequency (e.g., a genetic disorder like Tay-Sachs). At the top of the pyramid are the few cases of true uniqueness, which are by definition difficult, if not impossible, to identify in advance of chance discovery. **Assigning, a priori, a value to any one level is not possible since a commercial product can be developed from tissues and cells obtained from any level.** Finally, to an increasing degree, both the "uncommonness" of certain tissue at the intermediate level and the "rarity" of some specimens at the top level can be overtaken by technology. That is, rarity of the original sample is not the only important factor because as newer techniques develop, researchers are better able to detect novel substances or purify smaller amounts of known compounds. Once the peculiarities of the tissue or cell line have been identified and studied, biotechniques (e.g., gene cloning) provide a means to reproduce the peculiarity without further need of the material itself.

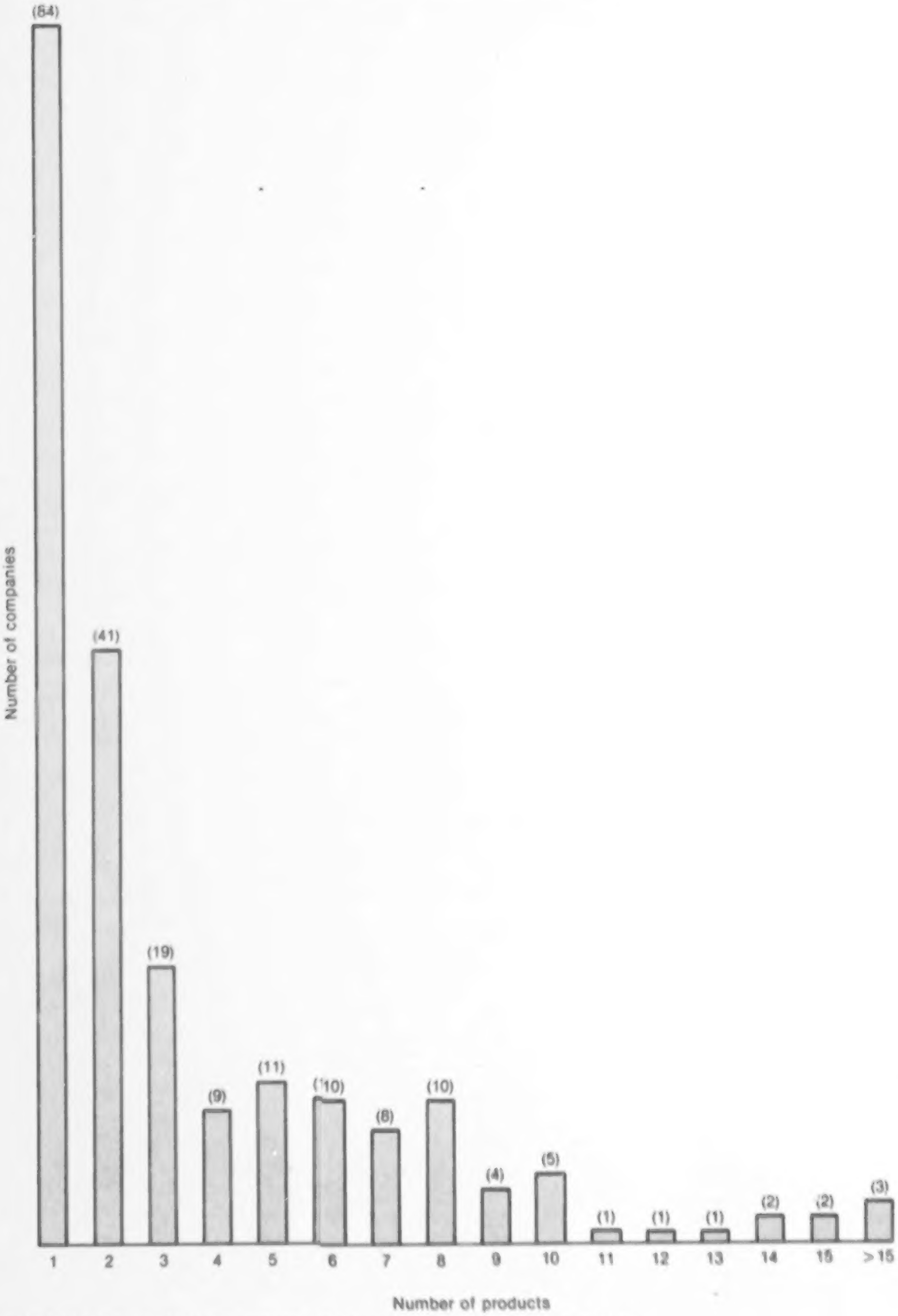
INDUSTRY

The biotechnology industry is a third major stakeholder in the controversy surrounding the use of human tissues and cells for financial gain. It is comprised of a variety of different types of organizations including the established pharmaceutical companies, oil and chemical companies, agricultural product manufacturers, and the new biotechnology companies. A detailed treatment of commercial biotechnology activities was published in 1984 by OTA (51); thus this section provides only a brief description of pharmaceutical-related biotechnology companies to give a sense of the current and projected levels of activity in the industry. This section also discusses the product development process.

The Companies

There are nearly 350 commercial biotechnology firms in the United States actively engaged in biotechnology research and commercial product development and approximately 25 to 30 percent appear to be engaged in research to develop a human therapeutic or diagnostic reagent (37). Many companies are developing several human therapeutic products (see figure 12). Most, but not all, of the human therapeutic products are derived from human tissues and cells, or human cell lines or cloned genes. (Most human diagnostic reagents are rodent-derived.)

Figure 12.—Number of Human Therapeutic Biotechnology Projects by Company



SOURCE: L.I. Miller, *Biotechnology Industry 1986 Fact Book* (New York: Paine Webber, 1986).

In addition to the commercial firms operating in the United States, there is a strong international component to the biotechnology industry, with numerous research and development arrangements and partnerships between American firms and firms in Japan and Europe. Recent financial statistics on the top 10 U.S. firms in the industry are provided in table 7.

Through 1985, no new biotechnology firm had reported annual sales over $100 million or net profits over $6 million. Revenues in the industry have come largely from contract research and research and development (R&D) partnerships, rather than product sales (7). Since 1980, the biotechnology industry has raised about $1 billion in corporate and public investments, excluding about $400 million in R&D limited partnerships (5). Nevertheless, many business analysts consider that the human biologicals market has come of age in the last 2 years, as witnessed by government approval for marketing of the industry's first commercial therapeutic products.

Table 8 is a business analysis of the human therapeutic products (many using human-derived material) most likely to be marketed in this country over the next 10 years. The industry as a whole is actively researching and developing over 100 different therapeutic products with commercial potential, as demonstrated in table 9. Again, many, but not all, of these products use human-derived material.

The established pharmaceutical industry's involvement in biotechnology indicates that biotechnology is viewed as commercially valuable. These established firms provide two significant advantages to fledgling, startup companies. First, the experience and long-term funding capacities of pharmaceutical firms are believed to be needed for the extensive product testing phases that must precede any commercial marketing of a human therapeutic product (57). Second, the professional sales forces of the pharmaceutical companies are seen as necessary for immediate, successful marketing of biotechnology products. Major multinational pharmaceutical firms based in the United

Table 7.—Financial Statistics for Selected Biotechnology Companies (as of Dec. 31, 1985)

Company	Annual sales ($ millions)	Net profits ($ millions)
Genentech (CA)	89.6	5.6
Cetus (CA)	45.9	1.4
Biogen (MA)	31.4	−19.1
Centocor (PA)	22.4	3.5
Amgen (CA)	19.8	−1.5
Genex (MD)	16.2	−15.9
California Biotech (CA)	9.6	−0.5
Collaborative Research (MA)	8.8	4.3
Molecular Genetics (MN)	8.3	−2.5
Intergrated Genetics (MA)	7.3	−3.7

SOURCE: Shearson Lehman Brothers, Inc. (reprinted in *The Economist*, Apr. 19, 1986).

Table 8.—Estimated U.S. Marketing Date for Some Human Therapeutic Products[a]

1982
Insulin
1983
1984
1985
Human growth hormone
1986
Interferon (alpha)
Orthoclone OKT-3
Hepatitis B vaccine
1987
Immunoagents
Immunocytotoxic agents
Immunotoxins
IMREG-1
Interferon (beta)
Interferon (gamma)
Proinsulin
Protein A
Tissue plasminogen activator
1988
Acylated plasminogen streptokinase complex
Alpha-1 antitrypsin
Calcitonin
Epidermal growth factor
Erythropoietin
Immunoradiotherapeutics
Interleukin-2
Superoxide dismutase
Vitamin E microemulsion
1989
Atrial natriuretic factor
Herpes vaccine
Hyaluronic acid (anti-inflammatory)
IMREG-2
Lipid emulsion
Protein C
Pro-urokinase
Tumor necrosis factor
1990
Bone morphogenic protein
Colony stimulating factor (alpha)
Colony stimulating factor (GM)
Colony stimulating factor (megakaryocyte)
Colony stimulating factor (granulocyte)
Colony stimulating factor (macrophage)
Human osteogenic protein
Interferon (gamma analogue)
Interferon (gamma fragment)
Interleukin-1 (alpha)
Interleukin-1 beta blocker
Lipocortin
Lung surfactant protein
1991
Factor VIIIC
1992
Angiogenin
Anti-inflammatory peptide
B-cell factors
Burst promoting activity
Colony stimulating factor (G-pluripoietin)
Factor IX
Fertility hormones (FSH, LH, and HCG)
Fibroblast growth factor
Tissue inhibitor of metalloproteinases
Urokinase-antibody conjugate
1993
1994
1995
Renin inhibitors

[a] Many, but not all, of these therapeutic products contain human-derived material.

SOURCE: L.I. Miller, *Biotechnology Industry 1986 Fact Book* (New York: Paine Webber, 1986).

Table 9.—Some Human Therapeutic Products Being Developed by the Biotechnology Industry[a]

Immune modifiers:
- Allogeneic effect factor
- B cell growth factors
- Burst promoting activity
- Colony stimulating factor (GM)
- Colony stimulating factor (alpha)
- Colony stimulating factor (granulocyte)
- Colony stimulating factor (macrophage)
- Colony stimulating factor (megakaryoctye)
- Colony stimulating factor (G-pluripoietin)
- Colony stimulating factor (other)
- D-glutamic acid, d-lysine conjugates
- Desacetylthymosin alpha-1
- IgE peptides
- IMREG-1
- IMREG-2
- Interferon (alpha)
- Interferon (alpha) receptor
- Interferon (beta)
- Interferon (gamma)
- Interferon (gamma analogue)
- Interferon (gamma fragment)
- Interferon (gamma) receptor
- Interferon analogue
- Interferon inducer
- Interferon-interleukin hybrid
- Interleukin-1 (alpha)
- Interleukin-1 (beta)
- Interleukin-1 antagonist
- Interleukin-1 receptor
- Interleukin-2
- Interleukin-2 analogue
- Interleukin-2 in liposomes
- Interleukin-2 receptor
- Interleukin-3
- Interleukin-4
- Lipocortin
- Macrophage activating factor
- Macrophage migration inhibiting factor
- Macrophage peptides
- Monoclonal antibodies to T cells
- Monoclonal antibodies to HLA antigens
- Monoclonal antibodies to Interleukin-2 receptor
- Orthoclone OKT-3
- Protein A
- Protein A analogue
- Suppressive factor of allergy
- Suppressor factor L
- Suppressor factor S
- Suppressor factors, other
- T cell suppressor inducer factor
- Tissue inhibitor of metalloproteinases
- XL factor
- XN factor

Anticancer therapy agents:
- Ampligen
- Angiogenin
- Angigogenesis inhibitor
- Anticellular factors
- Cytotoxic glycoprotein
- Detox
- Human endogenous regulatory factors
- Immunoagents
- Immunocytotoxic agents
- Immunoradiotherapeutics
- Immunotoxins
- Lectin
- Lymphotoxin
- Minactivin
- OH-1
- Oncostatin
- Ovamid
- Tumor growth inhibitor factors
- Tumor necrosis factor
- Tumor necrosis factor KBS

Blood proteins/enzymes:
- Acylated plasminogen streptokinase complex
- PEG-Adenosine deaminase
- Alpha-1 antitrypsin
- Antithrombin III
- Apolipoprotein-E
- PEG-Asparaginase
- PEG-Catalase
- Coagulation agents
- Elastase
- Elastase inhibitor
- Enzyme 1
- Enzyme 2
- Erythropoietin
- Factor VIIIC
- Factor IX
- Factor Xa
- Fibrinolytic agents
- Hementin
- Hemopoietin-1
- Hirudin
- Human serum albumin
- Lipoproteins
- Lung surfactant protein
- Lysozyme
- Protein C
- Pro-urokinase
- Renin inhibitors
- Renin monoclonal antibody
- Streptokinase
- Streptokinase complex
- Superoxide dismutase
- Superoxide dismutase analogue
- PEG-Superoxide dismutase
- Extracellular superoxide dismutase
- Tissue plasminogen activator
- Trypsin inhibitor
- Urokinase
- Urokinase antibody conjugate
- PEG-Urokinase
- von Willebrand factor

Hormones:
- Angiogenin
- Angiogenic factor
- Angiogenesis factor
- Atrial natriuretic factor
- Atrial natriuretic factor analogue
- Bone morphogenic protein
- Bone growth factors
- Calcitonin
- Calcitonin analogue
- Calcitonin gene related peptide
- Calcitonin precursor
- Cartilage inducing factor (a)
- Cartilage inducing factor (b)
- Connective tissue activator protein
- CNS growth factor
- Enkephalines
- Epidermal growth factor
- Fertility hormones
- Gonadotrophin releasing hormone
- Growth associated protein
- Growth hormone releasing factor
- Human growth hormone
- Hyaluronic acid
- Inhibin
- Insulin
- Insulin receptor
- Luteinizing hormone releasing hormone
- Nerve growth factor (beta)
- Neuropeptide Y
- Neurotransmitter agents
- Neurotrophic factors
- Oxytocin
- Parathyroid hormone inhibitors
- Platelet derived growth factor
- Proinsulin
- Prolactin-release inhibiting factor
- Relaxin
- Secretin
- Somatomedin C
- Somatostatin
- Somatostatin analogue
- Somatostatin peptides
- Tetragastrin
- Thyrotropin releasing hormone
- Transforming growth factor (alpha)
- Transforming growth factor (beta)
- Vasopressin

Other products:
- Chimeric antibodies
- Encapsulated islet cells
- Monoclonal antibodies against human proteins
- Vaccines for contraception
- Vaccine for Epstein-Barr virus-induced malignant lymphoma
- Vaccine for lung cancer
- Vaccine for melanoma

[a] Many, but not all, of these therapeutic products contain human-derived material.

SOURCE: L.I. Miller, *Biotechnology Industry 1986 Factbook* (New York: Paine Webber, 1986).

States budget between $300 million and $400 million annually for research and development (5).

Industrial Product Development

The Food and Drug Administration (FDA) requires a biopharmaceutical product to undergo a detailed process of research, development, and testing before the product can be marketed. Studies of the conventional pharmaceutical development process have shown that only about 12 percent of the drugs that enter the human testing process reach the marketplace, and that the testing process itself is lengthy and costly (24). The

Box C.—Angiogenin: A Case History From Research to Product Development

The research and development process that may lead to the commercialization of a product derived from human tissues or cells can be lengthy and can involve many parties. The following case history chronicles the development of one such product: angiogenin.[1] The events unfold over a period of almost eight decades and the final chapter (U.S. approval for marketing) is not yet complete. The story involves a patient with a tumor (the source); researchers in many laboratories; the biotechnology industry; and an university-industry agreement. It illustrates the complex process necessary to develop a biopharmaceutical derived from human tissues or cells.

Angiogenesis is the induction of the formation of blood vessels, a function known for some time to be critical to the process of expanding the network of capillaries and blood vessels that a tumor needs to grow and spread (3,15,18,20,22,26). The master molecule responsible for the phenomenon in humans had long been sought, but until 1985 the purification and characterization of this molecule had not been achieved (16). Some 200 laboratories worldwide are involved in angiogenesis research.

In 1985, the human protein that promoted angiogenesis in vivo was isolated and characterized. The investigators called the protein angiogenin. The protein was isolated from an established human cell line (called HT-29) that had been cultured 21 years earlier from the tumor of a 44-year-old woman (17). This cell line constantly secretes minute amounts of angiogenin, although researchers believe that the protein is also secreted at certain times by normal, nonmalignant cells. Isolating angiogenin was only the first step: if inhibitors to angiogenin can now be found and produced, it is possible that they could be used to starve tumors of their blood supply.

The search for the master molecule of angiogenesis was complicated. Researchers went through hundreds of liters per week of a special cell culture medium called tumor-conditioned medium. To obtain this special medium, the HT-29 cell line was grown in serum-free medium with the medium being siphoned off over time. The angiogenin was secreted into the tumor-conditioned medium at a yield of 0.5 micrograms per liter—this amounts to approximately one grain of salt in an entire liter of medium. After several months, enough purified substance was obtained to conduct a single experiment to determine the nature of the molecule. After determining the entire sequence of 123 amino acids in human angiogenin, the researchers proceeded with techniques to clone the gene for the angiogenin protein, thereby making it possible to prepare adequate quantities of the molecule.

Commercialization of an angiogenin-based product is not expected for at least 5 to 6 years (37,39). The research that resulted in the isolation and characterization of angiogenin was done at Harvard University Medical School and was commissioned in 1974 by Monsanto Co. under an 11-year, $23 million investment—through which Monsanto gains exclusive licensing rights to patented products developed under this arrangement (39).

Figure 13 traces some of the historical highlights leading to the purification of the molecule responsible for angiogenesis. Obviously, a great deal of time and the talents of many scientists were involved in solving this scientific puzzle. It is important to note that many related offshoots of angiogenesis research, including the process in nonhuman species, while not represented in the figure, were critical to the discovery of the master molecule. Additionally, such related research involved considerable manpower and money (2, 16,31,33,39,49).

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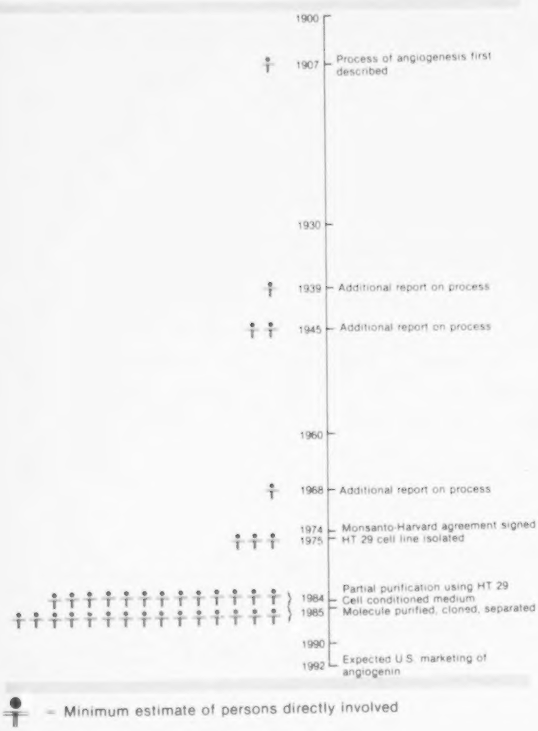
[1] For a recent review, see Folkman, J. and Klagsbrun, M., "Angiogenic Factors," Science 235:442-447, 1987.

Figure 13.—The Development of Angiogenin



SOURCE: Office of Technology Assessment, 1987.

cost associated with bringing a single new product to the marketplace is on the order of $65 million to $100 million (spread over several years or two to three decades) (4). In general, the biopharmaceutical product development process includes the following steps:

- **Research:** Identification and purification of the natural protein; characterization of the molecule, often including genetic engineering technology to produce the product.
- **Research and Development:** Improvement of product yield, initial formulation, and laboratory testing.
- **Development:** Formulation of the product into a pharmaceutical; preparation and scale-up of product manufacture.
- **Preclinical Testing:** Animal testing for acute or long-term toxicity and activity of the product.
- **Clinical Testing—Physician IND:** Human patient testing at one or more clinical centers where the actual application for testing has been filed by a physician, rather than the corporation.
- **Clinical Trials—Phase I:** Patient trials to determine drug safety and appropriate dosing schedules with only modest information regarding efficacy generated.
- **Clinical Trials—Phase II:** Broadened clinical patient trials to determine drug efficacy in one or more indications.
- **Clinical Trials—Phase III:** Advanced clinical patient trials to determine drug efficacy in one or more indications.
- **Product License Approval Filing:** Materials filed with the FDA to apply for marketing approval (36).

While it is difficult to predict whether all pharmaceuticals produced by biotechnology will emulate traditional pharmaceuticals, it is likely that standard government requirements for testing of pharmaceutical products will apply to all biotechnology products (51 FR 23309).

University-Industry Relationships

A critical aspect of the controversy surrounding the use of undeveloped human tissues and cells is the increasing overlap between the spheres of two of the interested parties: the research community and the biotechnology industry. University-industry research relationships in biotechnology assume a variety of forms, and these relationships are of relatively recent vintage. One estimate indicates that the total amount of money industry supplied to universities for biotechnology research in 1984 was about $120 million, accounting for 16 to 24 percent of all funds for biotechnology R&D available to institutions of higher education that year (11).

Faculty consulting and research relationships between individual professors and corporations can include:

- single or occasional visits and interchanges, informal collaboration;
- formal collaboration with or without consulting arrangements;
- consulting arrangements with or without formal collaboration (exclusive or nonexclusive); and

- formal exclusive relationships with understood financial commitments and patent rights.

Faculty may also be involved with scientific advisory boards for biotechnology companies and may be offered some type of restricted stock or stock options not generally awarded to external consultants.

Relationships between universities and corporations can include:

- corporate contributions, directed or undirected or in the form of fellowships;
- industrial procurement of particular services, for example, education and training or contract research;
- industrial affiliates;
- cooperative research;
- privately funded research centers, with either a single funder or multicorporate sponsors;
- long-term contracts, such as those between Monsanto and Harvard or Exxon and Massachusetts Institute of Technology;
- university-controlled companies set up to develop commercial potential from university research; and
- private companies that secure patent rights for resale (30).

The implications for a market in human specimens involving researchers, universities, university-industry partnerships, and industry are discussed in detail in chapter 7.

FEE-FOR-SERVICE RESEARCH

In addition to the commercial biotechnology firms and basic research members of the research community, a novel party that uses human tissues and cells has emerged. In 1984, the first for-profit company offering personalized cancer treatments was established in Franklin, TN. Biotherapeutics, Inc., was founded by R.K. Oldham, former director and founder of NCI's Biological Modifiers Program, and W.H. West, his colleague. A second branch in La Jolla, CA, is scheduled to open soon. It is a pioneer in what has been termed "fee-for-service" research: the company offers services to individuals who can afford to bear the costs of the research protocol involved in the cancer treatment (32).

As one part of its program, Biotherapeutics makes hybridomas producing monoclonal antibodies unique to an individual's tumor. These monoclonal antibodies are used with a mixture of other monoclonal antibodies (produced in response to tumors from other individuals) to treat the patient's tumor. The current cost of participating in the full service, not covered by conventional insurance policies, is $35,000. A $2,750 fee is charged for processing and preserving the patient's tumor for future use in therapy. Patient-funded research accounted for approximately 65 percent of Biotherapeutics' total revenues.

Biotherapeutics also uses interleukin-2, a lymphokine, to activate certain cells of the patient to become "lymphokine-activated killer cells." These cells can attack tumor cells in some individuals. The therapy regimens offered at Biotherapeutics are in use as experimental treatments elsewhere, particularly at NCI (32). Unlike other programs, however, patients at Biotherapeutics bear the cost of their individualized research/treatments. Persons contracting with Biotherapeutics waive all rights to "any cell line, reagent, product, approach, or properties that may be derived from tumor tissue, blood, or other specimens . . ." (8).

At present, Biotherapeutics is a unique combination of business, therapeutic institution, and research venture that uses human biological materials. About 200 patients have been treated at the Tennessee facility, and it is difficult to evaluate whether fee-for-service research companies will be an important interested party in the future.

SUMMARY AND CONCLUSIONS

In addition to scientific advances in biotechnology, the legal and economic considerations surrounding research on human biologicals have changed in the past decade. Many parties now have an interest in developing human tissues and cells: the source, the physician (or physician/researcher), the researcher, the university, and the biotechnology company. And, importantly, the spheres in which these parties operate are frequently intertwined—making resolution of conflicts difficult.

The ability to patent novel life forms created through biotechnology has spurred interest in developing human tissue and cells into marketable inventions. **The crucial element of patentability for most biological inventions in the United States, as shown in the *Chakrabarty* case, was the fact that the substance was in some way changed from the naturally occurring substance by human intervention**. This decision, coupled with technical advances in biotechnology, has resulted in increased interest in developing primary human biological material into marketable products.

Patients, healthy research subjects, and cadavers are all sources of undeveloped human tissues and cells, providing both normal and diseased specimens. As a general principle, sources of specimens are not paid for the types of samples most commonly used in biotechnology research. Volunteer research subjects, however, may be reimbursed for time or out-of-pocket expenses.

The research community, including both university and industry scientists, obtains human specimens for a broad spectrum of uses. These tissues and cells may be sought for single experiments as well as for the long-term development of cell lines or cloned genes. A sample might also be used directly to extract a commercial product. Researchers obtain human biological materials via many avenues, ranging from ad hoc agreements with local hospitals to federally supported collections.

In most cases, it is difficult to ascertain the contribution of any one individual's sample to a final commercial product. Moreover, because the process of research is a continuum, the expectation of developing a commercial product at the outset of research is extraordinarily small. Atypical human tissues and cells are sometimes discovered, however, and can be valuable to the R&D process of a marketable human commodity.

Recently, researchers and universities have sought innovative methods to fund research. The emerging presence of the biotechnology industry has become a logical partner in such research funding, and consequently a number of university-industry or investigator-industry arrangements have developed. These arrangements range from informal collaboration to formal contracting or funding.

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Chapter 5

Legal Considerations

"If biotechnologists fail to make provision for a just sharing of profits with the person whose gifts made it possible, the public's sense of justice will be offended and no one will be the winner."

—Thomas H. Murray
Congressional testimony, Oct. 19, 1985

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Chapter 5

Legal Considerations

As the use of human tissues and cells becomes more prevalent in biotechnology-related research and development, increased attention will need to be focused on the legal considerations of such use. Are tissues and cells property? If so, what right does a patient or research subject have in such materials? Does the provision of tissues and cells constitute the sale of a product or service?

No area of existing law definitely sets forth the rights held by an individual who provides tissues and cells to an academic or commercial researcher. No area of law clearly provides ownership rights with respect to human tissue and cell materials. Nor does any law prohibit the use or sale of human bodily substances by the living person who generates them or one who acquires them from such a person, except under certain circumstances. These circumstances relate to particular cell arrangements (e.g., organs, bodies) and uses (e.g., transplantation) that are not typically related to biotechnology research. Because neither judicial precedents nor statutes directly address the questions raised by the use of tissues and cells in research, the courts must do what common law judges have done for centuries; reason by analogy, using principles and precedents developed for other circumstances.

United States law has long protected people from those who would harm them physically or who would deprive them of full enjoyment of their property. Generally, this protection was afforded by the **common law**, the body of judge-made law built on judicial precedents. Common law has evolved over centuries, as judges have been called on to resolve disputes that have not been addressed by statute. Congress and State legislatures have enacted a variety of **statutes** to codify, modify, and overrule the common law. Today, while statutes specify many of our legal rights and duties, common law remains the basis for our legal principles, and common law analysis and reasoning forms the basis for our techniques of statutory interpretation.

INJURIES TO PERSONS v. INJURIES TO PROPERTY

The common law classifies many injuries for which recovery is permitted as either injuries to **persons** (which are analyzed under tort law principles) or injuries to **property** (which generally are within the domain of property law). Contracts can be made with respect to both persons and property, although certain types of contracts and contractual remedies are permitted with respect to property but not human beings.

Personal Rights

The common law gives individuals various "personal" rights to exclude others from interfering with their physical and mental integrity. Many invasions of bodily integrity are subject to criminal penalties; in addition, the common law tort of battery allows for recovery for physical and mental damages resulting from harmful or offensive physical contacts.

Invasions of physical autonomy are permitted only in those few situations where either individual or public interests (particularly health) would be substantially and justifiably benefited by a modest encroachment on individual autonomy. Examples of legally permissible invasions of physical integrity include laws compelling vaccinations; blood tests for marriage licenses; and blood and urine sampling of suspected criminals, military service, and penal service.

Although the law clearly affords people substantial means of protecting themselves from harmful or offensive physical contacts, the extent to which people can use their bodies is less clear. State law generally prohibits disfigurement, prostitution, and drug use. Federal law reflects similar policies and recently has added a new prohibition against organ sales (Public Law 98-507). These restrictions rest on concerns about individual health, public health, and public moral sensibility.

Property Rights

Property is generally viewed not as a single indivisible concept but as a bundle of legally protected interests, including the right to possess and use, to transfer by sale or gift, and to exclude others from possession. Although the property concept can be invoked to protect various legal interests, one's right to use property is commonly limited to uses that do not offend public safety or sensibilities. For example, a person may own a car but not have a right to use it without first obtaining a driver's license.

Nevertheless, the term property introduces certain economic and market connotations and calling the body property may act to make the use of market incentives with respect to the body and its parts more acceptable. Alternatively, if human tissues and cells are not characterized as property but as a severed part of a person, then tort law principles would still provide certain rights with respect to one's tissues and cells (e.g., right to privacy, right to adequate disclosure to give an informed consent). However, a right to buy or sell would probably not be among the rights provided.

In the absence of clear legal restrictions, the sale of tissues and cells is generally permissible unless the circumstances surrounding the sale suggest a significant threat to individual or public health, or strong offense to public sensibility. But while the law permits the sale of such replenishing cells as blood and semen, it neither endorses such transactions nor does it often characterize such transactions as involving property. In this sense, either permitting or forbidding the sale of human specimens by patients and research subjects can be claimed to be consistent with existing law.

The broad array of legal principles that might have implications for the use of tissues and cells in biotechnology (table 10) are discussed in the following section.

Table 10.—Possible Sources of Rights Relating to Human Biological Materials

Law of Patents
Law of Cadavers and Autopsies
Property rights in corpses
Emotional distress caused by wrongful acts toward cadavers
Law of Organ Transplantation
Donation of organs for transplantation
Sale of organs for transplantation
Law of Blood and Semen Sales
Sale of blood and semen
Product liability generally
Implied warranties under the Uniform Commercial Code
Specific performance under the Uniform Commercial Code
Blood as a product for tax law purposes
Law of Copyright
Law of Trade Secrets
Law of Conversion and Trespass to Chattel
Property interest
Possession
Injury to plaintiff
Abandonment
Res Nullius
Law of Accession
Cases involving crops
Specification

SOURCE: Office of Technology Assessment, 1987.

POSSIBLE SOURCES OF RIGHTS

Law of Patents

Patent law has direct application to biotechnology research and development. The Constitution gives Congress the power "[T]o promote the Progress of Science and useful Arts" by securing to inventors exclusive right to their inventions (Article 1, Section 8, Clause 8). Because patents convey exclusive rights to their holders, they are personal property (35 U.S.C. 261).

Under U.S. law, inventions belong in the first instance to their inventors. An employed inventor is ordinarily obligated to assign his invention to his employer under the "hired to invent" doctrine and by express provision in his employment agreement. Patents obtained by researchers thus generally are assigned to the institution funding the research.

A patent may be granted on any new, useful, and nonobvious composition of matter, or article of manufacture, machine, or process (35 U.S.C. 101-103). In 1980, the Supreme Court held in *Diamond* v. *Chakrabarty* that the mere fact that subject matter is "living" does not render it unpatentable (36). "Products of nature," however, are unpatentable because they lack novelty. The biological inventions being patented today are not crude, unaltered products of nature. A claim to the entire genetic material of a single cell would be rejected; but one may properly seek a patent on an isolated gene encoding a protein of interest.

The obviousness of a product is another bar to its protection by patent. Patent law creates a three-step test to determine whether an invention meets the non-obvious test for patentability (35 U.S.C. 103). This analysis consists of three factual inquiries concerning the prior art, that fund of information which is available or accessible to the public (81): 1) the scope and content of the prior art, 2) the difference between the prior art and the patent claims at issue, and 3) the level of ordinary skill in the pertinent art. If the claims in the patent would have been obvious, in view of the prior art, to a person having a level of ordinary skill in the pertinent art, then the patent is deemed obvious and does not meet the requisite criteria for patentability. For example, a patent on vitamin C (purified from lemon juice crystals) was denied because "lemon juice has been known for ages as a satisfactory specific for scurvy." But a patent on adrenalin crystals was held valid in view of the dangerous side effects of dried gland extracts of lesser purity (71,102).

While it is clear that researchers may alter donated tissues and cells into a patentable invention, patients and research subjects who contribute cells to research will not be considered inventors. Typically, the person providing the material will not make any suggestion regarding the use of the cells, or of the means for using them. While the patient's cells may have some novel characteristic, it is unlikely that the characteristic was appreciated by the patient.

The case law on what constitutes an act of invention has developed through interpretation of various provisions of the patent law. Under a section of the patent statute relating to who of several claimants is the true inventor, the inventive process is divided into **conception** (an outwardly manifested mental act), **reduction to practice** (a physical demonstration of practicability, or the filing of a well-framed patent application) and **diligence** (efforts to reduce a conception to practice) (35 U.S.C. 102(g)).

Conception means that the person claiming to be the inventor thought of both the desired result and the means for achieving that result, that means being an operative form of the invention claimed. Conception must be manifested by exterior acts or declarations that disclose the conception in a form enabling a person of ordinary skill in the art to practice the invention without the exercise of the inventive faculty (80).

In *Brenner* v. *Manson* (14), the Supreme Court held that a patent cannot be obtained on a method of producing a novel composition unless the composition has a practical (nonresearch) utility. One patent law book states that, based on the context of the case, "a necessary implication of *Brenner* is that discovery of the utility is part of the act of inventing" (29). The Patent Office apparently agrees (34).

If contemplation of a nonresearch utility is a necessary part of conception, then the patient's or research subject's assertion that tissues have a value in research is not a conception unless there is recognition of a practical use for those tissues, or their derivatives, outside research. Besides appreciating the utility of the cells, the patient or research subject must also appreciate that the cells are novel. In a case involving a chemical invention, for example, a plaintiff who accidentally produced a particular catalyst but did not recognize that it differed in form from the prior art was held not to conceive the new catalyst (43). The rule that "there is no conception or reduction to practice where there has been no recognition or appreciation of the existence of the new form" was acknowledged in *Silvestri* v. *Grant* (86), but led to a different holding since Silvestri had recognized that ampicillin II was different from ampicillin I, even though he had not recognized its superior stability.

Law of Cadavers and Autopsies

Property Rights in Corpses

The earliest Anglo-Saxon cases to consider ownership of human tissue—specificially, corpses—were decided almost 1,000 years ago by special ecclesiastical courts in England. Established by William the Conqueror, the church courts were completely independent of the civil courts and were eventually given complete jurisdiction over all matters concerning burials and disposition of corpses (49). With few exceptions, control of dead bodies remained within the exclusive jurisdiction of the church courts until the 19th century, when the growth of medical schools and their need for cadavers for dissection created a challenge to ecclesiastical dominion over bodies (85).

In colonial America, the absence of ecclesiastical courts resulted in civil jurisdiction over bodies and the application of common law principles. There were no commercial rights in cadavers, no right for a decedent to direct the manner of burial, and no burial rights enforceable by the next of kin. The refusal to create commercial rights was unquestionably based on religious and moral tradition. The absence of property rights led to the other rules, following the common law principle that courts should only be concerned with commercial considerations and not with sentimental concerns.

During the 1800s, it became apparent that the strict common law doctrine was inequitable and courts began assigning to the next of kin an enforceable right to possession of a body for burial. To preserve the continuity of common law principles, the right was sometimes characterized as a "property right" (49). This right became so well established that in 1891, a court suggested that the "fact that a person has exclusive rights over a body for the purposes of burial leads necessarily to the conclusion that it is his property in the broadest and most general sense of the term" (59).

Judicial references to property rights in corpses were misleading, however. While common law property rights generally include the right to possess and use, to transfer by sale or gift, and to exclude others from possession (15), few of these rights were applied to bodies: the theft of a cadaver was not larceny, the sale of a cadaver was a common law crime, the heirs had no right to repossess a body wrongfully taken from them, and a cadaver could not be the subject of a lien.

Recognizing the limited applicability of property law to corpses, 20th century American courts retreated from the broad pronouncement of bodies as property and began referring to more limited "quasi-property rights" vested in the next of kin and arising out of their legal duty to bury the dead. These rights include the right to possession and custody of the body for burial, the right to have it remain in its final resting place, and the right to recover damages for any outrage, indignity, or injury to the body of the deceased (1). The family's interest in the dead body was subject to various interests of the State government, including concern for public sensibility, promotion of public health, identifying cases of murder, and protecting the economic interests of undertakers and insurers.

Quasi-property analysis became the prevailing rule in both the United States and England during the early 20th century and continues to be applied to disputes over funeral arrangements (61).

Emotional Distress Caused by Wrongful Acts Toward Cadavers

In the 1930s, American jurists and legal scholars began questioning the applicability of property law concepts to cases involving wrongful conduct toward corpses. Gradually, the newly developing tort law framework of intentional infliction of emotional distress (also called "outrageous conduct") was viewed as a more appealing theoretical basis for a legal claim based on unauthorized retention of body parts and other forms of wrongful conduct. As William Prosser stated in *Law of Torts*:

> There are a great many cases involving the mishandling of dead bodies, whether by mutilation, disinterment, interference with proper burial, or other forms of intentional disturbance. In most of these cases the courts have talked of a somewhat dubious "property right" to the body, usu-

> ally in the next of kin, which did not exist while the decedent was living, cannot be conveyed, can be used only for the one purpose of burial, and not only has no pecuniary value but is a source of liability for funeral expenses. It seems reasonably obvious that such "property" is something evolved out of thin air to meet the occasion, and that it is in reality the personal feelings of the survivors which are being protected, under a fiction likely to deceive no one but a lawyer (77).

Today, cases concerning wrongful acts toward a dead body are generally treated as tort cases rather than property disputes. The American Law Institute's most recent *Restatement of Torts*, which describes the general principles of American tort law, states that one who intentionally, recklessly, or negligently removes, withholds, mutilates, or operates on the body of a dead person, or who prevents its proper interment or cremation, is subject to tort liability to a member of the family who is entitled to disposition of the body (4). The cause of action is a personal right of the survivor rather than a right of the decedent or his estate, since the courts are not primarily concerned with the extent of the physical mishandling or injury to the body per se, but rather with the effect of such improper activities on the emotions of the surviving kin (6).

It is important to note that to be actionable, the emotional distress must be genuine, not theoretical. If the plaintiff does not learn of the offensive conduct, or learns of it but is not distressed as a consequence, there is no basis for suit. Also, except in cases where the defendant has knowledge of the plaintiff's peculiar susceptibility and practices despite this knowledge, the distress must be of a nature that a reasonable person of "ordinary sensibilities" would also experience under the circumstances (77). A plaintiff must therefore show both subjective and objective elements of emotional distress.

Applicability to Cases Involving Human Tissues and Cells

Society's traditional refusal to allow commercial rights in cadavers or dead body parts suggests that a claim for property rights in living body parts could be judicially rejected as failing to state a cause of action. The burden would be on the party claiming such rights to demonstrate that the biological, economic, social, and ethical differences between dead and living specimens are more important than their similarities, and that living human specimens merit protection as a result of these differences.

As mentioned earlier, there are noncommercial quasi-property rights in a cadaver that arise out of the legal duty placed on survivors to bury their dead (1). The kin's duty to bury the dead appears to be irrelevant to research or commercial uses of biological materials from living sources, so any rights derived from such a duty would have little relevance.

The emotional distress theory provides a useful legal framework in cases where biologicals were obtained or used wrongfully, since the basis for the tort is the wrongfulness of the conduct and its effect on the living rather than property law concepts. To fulfill the legal requirements of the tort, the physician's conduct would probably have to demonstrate willful and wrongful disregard for the express or implied desires of the patient and that the conduct resulted in severe emotional distress. In one case, for example, a woman gave birth to a premature baby who died shortly thereafter. Several weeks later, through an unusual course of events, a hospital employee showed the mother a jar containing the infant's body. The mother suffered various physical and psychological injuries as a result and was awarded $175,000 in damages for the tort of "outrageous conduct" (41,52).

Variables Affecting Emotional Distress Claims

A plaintiff in an emotional distress case involving the use of human tissues or cells in research must prove two fundamental facts to prevail. First, the physician or researcher must have acted wrongfully. Acts that could be considered sufficiently wrongful in their disregard for the plaintiff's feelings include:

- using an individual's specimens in research without consent,
- misrepresenting the purpose of diagnostic or medical procedures when they are performed

solely for the purpose of obtaining specimens, and

- suggesting to a patient that refusal to donate specimens for research will affect the availability or quality of medical care.

All of these acts are related to the physician's or researcher's duty to disclose information to the patient or research subject and to obtain consent. The generally accepted standards of professional medical conduct are described in chapter 6.

Second, the plaintiff must also prove that substantial emotional distress—both objectively and subjectively—was suffered as a result of the wrongful act. While these factors will vary from case to case, a few generalizations can be made, particularly about the objective element that examines whether a "reasonable person" would be emotionally disturbed by the conduct.

Whether emotional distress can be shown is related to variables such as the **type** of biological material involved, the **use** to which the specimen is put, the **method** of procuring the specimen, and the **knowledge** of the attending physician or end-user. In addition, these variables may affect the size of consequential damage awards, which are based on the degree of the emotional stress and its effect on the patient's life, health, happiness, and pocketbook. These factors are also relevant in determining whether the wrongful conduct was so reprehensible that a court will permit the plaintiff to seek an additional (punitive damage) award, beyond actual damages, to punish the offender and create a strong deterrent for future wrongdoing.

It may be especially upsetting to patients when certain **types** of biological materials are involved. For instance, most patients will probably have greater emotional sensitivity about research using their organs, limbs, or brain cells than research using their fingernail clippings, hair, blood, urine, or sweat. The enhanced sensitivity might be due to the fact that the former types of biological materials were especially important to the patient's well-being prior to removal, or because they are generally nonrenewable, or because they were removed using more invasive and traumatic techniques.

Similarly, the **use** to which a specimen is put may affect the patient's emotional reaction, particularly if the patient has religious or moral beliefs that conflict with the use. For instance, some people consider altruistic gifts of human tissues and cells to be less offensive than profitable exchanges. This is illustrated by the altruistic motivation that spurs most blood donations despite the legal permissibility of selling blood. For those who believe that altruism is the only proper motivation for transactions involving human biologicals, it would be less objectionable to them if their physician donated a specimen to biomedical researchers than if he sold it for a profit to those same researchers.

For other individuals, sales of biological materials might be permissible for some uses but not for others: one might agree to sell one's hair for use in a wig but not in a voodoo doll. Thus, selling placentas to shampoo manufacturers for use in formulating hair care products (which several hospitals allegedly did in the 1960s, causing substantial public outrage) is probably more egregious than selling them to scientists for research to reduce infant mortality. Similarly, some people may find some forms of research objectionable but not others.

The degree of emotional distress may also vary with the **method** of procurement. For example, a doctor who solicits and uses a urine sample for diagnostic purposes and who later uses the specimen in research may have acted wrongfully if he did not first obtain the patient's consent for research. However, any consequential emotional distress may not be actionable, unless it is shown that the physician acted outrageously, recklessly, wantonly, or willfully, or because a reasonable person of ordinary sensibilities would not experience serious emotional effects as a result.

A deception accompanied by an invasive or painful medical procedure is probably even more offensive. If the specimen obtained in the preceding example was not urine but bone marrow, the resulting emotional distress would probably be more severe. In addition, the plaintiff would be entitled to collect for his physical pain and suffering during and as a result of the extraction procedure if it was proven that the physician was also liable for battery due to invalidation of the patient's consent to the procedure.

The **knowledge** of those who procure the specimen would also have an effect on culpability since the tort generally requires an outrageous act and not merely a negligent one. As mentioned earlier, knowledge of the peculiar emotional susceptibilities of a patient can lead to liability where it otherwise would not exist. Early emotional distress cases dealing with dead bodies, for example, held that unauthorized embalming of a corpse was not actionable unless the mortician knew that the decedent's religious beliefs forbade embalming (7). Similarly, a patient who is distressed by an incident that would not distress a person of ordinary sensitivities would not be entitled to sue unless the physician knew that the patient was unusually squeamish and the doctor therefore should have foreseen the deleterious consequences of his act. Thus, a pyrophobic patient whose leg was amputated and cremated was not permitted to recover damages for the mental anguish he claimed he suffered as a result of the cremation because the hospital staff did not know of the patient's phobia and had not acted unreasonably by disposing of the limb through the usual method (16).

Law of Organ Transplantation

Donation of Organs for Transplantation

In the mid-20th century, scientific advances led to an increasing need for transplantable tissue. From 1947 until 1968, 40 States enacted statutes permitting anatomical donations from cadavers for transplantation or scientific research (85). Variations among the statutes lead to the formation of a special committee of the Commissioners on Uniform State Laws to draft a uniform donation statute. The result of this effort is the Uniform Anatomical Gift Act (UAGA) which, after receiving final approval from the commissioners in 1968 (94), has been adopted throughout the 50 States and the District of Columbia (82). The UAGA supersedes only those areas of the common law of cadavers that are addressed by the act.

The UAGA permits any competent adult to make a gift—to take effect upon death—of all or any part of his body for purposes such as medical education, research, and transplantation. Donations for research purposes may only be made to hospitals, physicians, medical and dental schools, and tissue banks. Post mortem donations of human tissues and cells to noncommercial biomedical researchers are therefore permitted, although transfers from noncommercial researchers to commercial researchers are not addressed by the model law. Organs removed during surgery are not gifts, because the donative intent required for a legal gift generally is lacking (44).

Gifts may be made either by will or by a gift document such as a donor card. In the absence of contrary instructions by a decedent, the next of kin may authorize a gift. Recipients may accept or reject the gift, and a researcher who removes or accepts an organ in good faith in accordance with the terms of the UAGA is not liable for civil damages or subject to criminal prosecution.

It has been argued that the UAGA recognizes rights in the human body that may be classified as property rights (64). However, the UAGA does not discuss inter vivos (during life) gifts, nor does it say anything about the sale of organs or other body parts. The chairman of the committee that drafted the UAGA has written that it was intended neither to encourage nor prohibit sales (87).

As a result of ethical concerns raised by reports of impoverished Americans offering to sell a "spare" kidney or cornea (typically for $10,000 to $50,000) (57) and physicians offering rewards or finder's fees for acceptable organs (25), a few States have passed laws expressly prohibiting remuneration to living or dead organ donors (35). In the majority of States, however, a donor is apparently able to make a legal contract to sell a part of his body, unless the biological transfer is to take place after death and the common law provisions on cadaver disposition are held to forbid such a sale (69).

Sale of Organs for Transplantation

In 1984, Congress enacted the National Organ Transplant Act (NOTA; Public Law 98-507). NOTA prohibits the sale of a human kidney, liver, heart, lung, pancreas, bone marrow, cornea, eye, bone, and skin. Although the act makes it a felony to purchase specified human organs for transplantation, reasonable payments for a living donor's expenses (e.g., travel, housing, and lost wages) are permitted. NOTA's prohibition does not apply to sales of human tissues and cells for research, commercial, or other nontransplantation purposes.

The statute's organ sale prohibition was based primarily on congressional concern that permitting the sale of human organs might undermine the Nation's system of voluntary organ donation (102). It was also driven by concern that the poor would sell their organs to the rich, to the detriment both of poor people who might feel economically coerced to become organ suppliers and those who need but cannot afford transplantable organs. It may also reflect congressional distaste for sales of human body parts generally. The considerations that mitigate against the sale of organs for transplant may or may not apply to the sale of other human tissues and cells for research and development (37).

Law of Blood and Semen Sales

Sale of Blood and Semen

No State or Federal statute prohibits the sale of blood, plasma, semen, or other replenishing tissues if taken in nonvital amounts (69). Nevertheless, State laws usually characterize these paid transfers as the provision of services rather than the sale of a commodity, either in the State's version of the UAGA or in their version of the Uniform Commercial Code (UCC), which governs various commercial transactions including contracts for the sale of goods (95).

The primary legal reason for characterizing these transactions as involving services rather than goods is to avoid liability for contaminated blood products under either general product liability principles or the UCC's implied warranty provisions. In addition, services are not subject to the UCC's specific performance provisions.

Product Liability

Product liability is the name given to the area of law involving the liability of suppliers of goods or products for the use of others, and their responsibility for various kinds of losses resulting from defects in those products. Four possible theories of recovery are available under the complexities of modern product liability law:

- strict liability in contract for breach of an express or implied warranty,
- strict liability in tort largely for physical harm to persons and tangible things,
- negligence liability in contract for breach of an express or implied warranty that the product was designed and constructed in a workman-like manner, and
- negligence liability in tort largely for physical harm to persons and tangible things (78).

Generally, negligence liability may exist with respect to both products and services, but strict liability is applicable only to products. Thus, characterization of blood and semen sales as services enables blood and semen banks to avoid liability when a specimen was defective (e.g., contaminated or infected) if the bank was not negligent in its handling of the specimen (55).

Implied Warranties Under the UCC

If sales of tissues and cells were to be treated as sales of goods as opposed to sales of services, then UCC warranties would be applicable. The UCC provides that commodity contracts (but not service contracts) are subject to two implied warranties:

- the **implied warranty of merchantability** requires goods to be of "fair average quality" within the description provided by the seller and fit for the ordinary purposes for which such goods are used (97), and
- the **implied warranty of fitness** requires goods to be suitable for the buyer's particular purpose to the extent this purpose is known by the seller (98).

The merchantability warranty only applies to sales by "merchants," defined by the UCC as those who regularly supply the product (e.g., hospitals, tissue banks) but not occasional sellers (96). The fitness warranty applies equally to regular dealers and occasional sellers (98).

If transactions for blood or semen were treated as sales of commodities, these implied warranties could result in substantial liability for injuries resulting from transfusion or insemination with a specimen infected with hepatitis, AIDS, or another contagious disease. Insemination with sperm containing a genetic defect could also result in substantial liability. Since liability would be based on strict liability for breach of warranty rather than negligence principles, careful examination of specimens for contamination or a genetic flaw would not entitle the providing entity to avoid liability if an injury occurred.

Alabama has added a subsection to its UCC as follows:

> Procuring, furnishing, donating, processing, distributing, or using human whole blood, plasma, blood products, blood derivatives, and other human tissues such as corneas, bones or organs for the purpose of injecting, transfusing, or transplanting any of them in the human body is declared for all purposes to be the rendition of a service by every person participating therein and whether any remuneration is paid is declared not to be a sale of ~~such whole~~ blood, plasma, blood products, blood derivatives, or other human tissues (8).

The amendment prevents recovery on a breach of warranty theory where a plaintiff contracts a disease such as hepatitis as a result of a blood transfusion (88). Other State courts have reached the same conclusion as Alabama by judicial interpretation (26), while other States have enacted statutes specificially exempting hospitals and blood banks from liability for disease transmitted by transfused blood without amending the official text of the UCC (9).

If exchanges involving human tissues and cells are treated like those involving blood and semen—i.e., if such exchanges are considered to be transactions for services rather than commodities—then certain types of liability may similarly be avoided by tissue and cell banks, research institutions, hospitals, and companies. While liability would continue to exist for negligence (e.g., failing to use an available and appropriate test to screen suppliers for viral infections) there would be no liability for imperfect specimens in the absence of negligence.

Specific Performance Under the UCC

The UCC and the common law of contracts provide that if a seller breaches or repudiates a contract, the buyer may recover monetary damages or, under appropriate circumstances, seek an injunction compelling **specific performance** (fulfillment of the contract according to its precise terms) (99). Generally, specific performance may be decreed if the goods are unique or in other circumstances where monetary damages are inadequate to make the buyer whole (100).

If a transaction in human tissues or cells is treated as **the sale of goods**, the UCC provides a possible remedy for the buyer, since it "seeks to further a more liberal attitude than some courts have shown in connection with the specific performance of contracts of sale" (102). However, a contract to **render personal services** will not be specificially enforced because it is undesirable to compel a continued personal association after disputes have arisen and confidence and loyalty are gone. In some instances, such imposed associations may seem like involuntary servitude, which is unconstitutional (2,48).

A 1978 case involved the forced donation of bone marrow to a man with aplastic anemia by his genetically compatible cousin (62). Initially, the healthy cousin agreed to undergo tests to determine his suitability as a donor. Early tests showed him to be a good match, but he failed to appear for additional confirmatory tests and refused to donate any bone marrow. The ill cousin sought an injunction that would have forced the healthy cousin to undergo the confirmatory tests and to donate bone marrow if found to be sufficiently genetically compatible. The court denied the injunction, saying "(f)orcible extraction of living body tissues causes revulsion to the judicial mind. Such would raise the specter of the swastika and the Inquisition, reminiscent of the horrors this portends (62)." While the case was argued on equitable rather than contractual grounds, the court's abhorrence to coerced tissue donations might apply with equal force to a repudiated contract for human tissues and cells.

Blood as a Product for Tax Law Purposes

State laws usually characterize payment for blood as for the provision of services rather than the sale of a commodity. However, this characterization has not been applied consistently in the tax treatment of such transactions. The Tennessee Supreme Court has held that whole blood is an item of tangible personal property subject to a State sales tax (51,72). An Alabama court has indicated that it would have preferred to make a similar holding on the sales tax issue had it not felt constrained by the language in the Alabama version of the UCC to rule otherwise (88).

In an income tax case, a Federal appellate court considered whether the sale of blood is a service or a product (104). While the case was decided on due process grounds rather than on the basis of the property versus services distinction, the case suggests that "blood plasma . . . is tangible property which in this case commanded a selling price dependent on its value."

Law of Copyright

Copyright provides protection for "original works of authorship fixed in any tangible means of expression" (17 U.S.C. 102). Works of authorship include literary, musical, dramatic, choreographic, pictorial, graphic, sculptural, and audiovisual works (17 U.S.C. 102(b)). Copyright protection, however, does not attach to any idea, procedure, process, system, method of operation, concept, principle, or discovery. Copyright provides an author with exclusive rights for the specific form of expression, but not for the underlying idea.

One writer on intellectual property law topics has suggested that DNA molecules are copyrightable as express "information," albeit genetic information. To him, bases are letters; codons are words; and genes are sentences. Switching metaphors, he compares DNA molecules to computer programs; both are sets of instructions (53).

Others have challenged these views as based on false analogies (31). In any event, these arguments would not, even if fully accepted, confer copyright protection on human biological materials other than DNA. Even if DNA were copyrightable, a patient probably could not claim to be its author because the patient exercises no conscious control over the sequence of bases. Thus, to the extent that copyright protection is available, it would be applied solely to recombinant DNA as a composite work.

Law of Trade Secrets

The precise source of trade secret rights is a matter of dispute. Some consider trade secrets to be intangible property. Others regard trade secrets as merely information subject to restrictions on disclosure and use as a result of express contract provisions, or by operation of law in view of the trust and confidence reposed in the recipient by the discloser (50). Since a trade secret is rooted in secrecy, publication impairs the legal right to control disclosure and use. Unlike a patentee, a trade secret owner has no recourse against a later independent developer, or even one who discerns the secret by analysis of the products placed on the open market by the owner. Only the abuse of a confidential relationship creates liability.

Liability may flow from a statute or a contract (express or implied) between the parties. In making theft of a trade secret unlawful, a number of State criminal laws include cultures and microorganisms among the types of articles which may represent a trade secret (23,30,40,46). Recently, patent attorneys at one company published some suggested confidentiality agreements for use in disseminating biological materials. The most detailed of these agreements addressed the following issues:

- When the recipient is a university researcher, how should responsibilities be apportioned between the researcher and his or her university?
- What types of biological material are covered? In particular, what modification of the material might take it outside the agreement?
- To whom may the material be transferred?
- How may the material be used?
- Is the researcher free to publish his/her work?
- Does the recipient have an obligation to disclose his/her work to the supplier in advance of publication?
- If the work is patentable, what recognition will be given to the supplier's contribution?

- Is the transfer a sale or a license?
- Is the material warranted in any way?
- Who will bear liability for any harm arising from use of the material (54)?

A sample of human tissues and cells is not itself a trade secret (73), but may be characterized as a tangible article representing an intangible trade secret (65). Still, unless the patient contemplated, at the time of transfer, that the excised tissues or cells had commercial value, it would be difficult to argue that the biological material represented a "trade secret" of the patient. Because a trade secret is information used in one's business, a patient must be in the business of selling or using those tissues or cells in order to hold a trade secret. Under the more liberal Uniform Trade Secrets Act, use in business is not necessary, but reasonable efforts by the patient to maintain the secrecy of the tissue still would be required to retain trade secret status. Permitting a researcher to publish a description of the tissue would seem antithetical to recognition of a trade secret therein.

Law of Conversion and Trespass to Chattel

Personal property is protected by both criminal and civil law. The theft of property is a crime known as larceny. Interference with another's property is the tort of trespass to chattel, or conversion, depending on the severity of the interference.

The tort of "trespass to chattel" occurs when one person intentionally interferes with someone else's personal property. However, to prevail in a trespass claim the owner must show he suffered some actual damages as a result. Establishing actual damages could be extremely difficult for an individual whose biological materials had been removed from the body for a diagnostic or therapeutic purpose. Furthermore, damages are limited —a plaintiff can only recover for the actual loss in value of the property caused by the interference.

For these reasons, a plaintiff seeking remuneration for use of biological substances would more likely claim that **conversion** has occurred. This tort has been defined as "an intentional exercise of dominion or control over a chattel which so seriously interferes with the right of another to control it that the actor may justly be required to pay the other the full value of the chattel (3)." Thus the potential recovery for a plaintiff in a conversion suit (full value of the property) can be much greater than in a claim only alleging trespass (actual damages to the property).

Hundreds of decisions involving the tort of conversion have been decided over the last several decades. Because tort law is determined primarily by individual States, and not by Federal law, significant variation in the conversion doctrine exists from State to State. Federal courts trying conversion cases usually apply the law of the relevant State. Because of a lack of uniformity in State conversion laws, the outcome of suits alleging conversion of biological substances would depend partly on the specific laws of the State whose law is being applied. Nevertheless, some general principles can be distilled from the different State and Federal cases. One analysis of tort law suggests that the following factors should be considered by a court in determining whether conversion has taken place:

- the extent and duration of the actor's exercise of dominion or control,
- the actor's intent to assert a right in fact inconsistent with the other's right of control,
- the actor's good faith,
- the extent and duration of the resulting interference with the other's right of control,
- the harm done to the chattel, and
- the inconvenience and expense caused to the other (3).

Property Interest

The essence of the tort of conversion is interference with the owner's right of possession or control. The plaintiff in a conversion suit must therefore show a right to possess the property or the suit will fail. Historically, establishing a property interest in a bodily part has been quite difficult. As discussed earlier, the sale or disposition of cadavers, cadaver tissues, or the cadaver organs has generally been restricted.

Perhaps the most direct support for a patient's property claim in tissue comes from State criminal statutes defining property. Listing the types of articles protected against larceny, a number of States have specificially included cultures and micro-organisms (23,30,40,46). A patient residing in such a State could cite the statute as evidence of a legislatively recognized property interest in cultures made from excised patient tissues and cells.

Possession

To successfully bring a claim of conversion, a plaintiff must be "entitled to immediate possession of the chattel" (13,30). Without this clear right to possession, there is no tort of conversion. For example, an owner who leases equipment to another cannot bring an action against a third party for conversion during the lease period because the owner has no immediate right of possession (10). Similarly, a right that is contingent on future events will not support a claim for conversion (70,76). The individual's right to possession must therefore exist at the time the biological material is removed, and not arise months or years later when the substance has been shown to be commercially valuable.

Whether a person whose biological material is incorporated into a bioengineered product could be able to meet the test of possession is not altogether clear. Often, the material used by a researcher has been removed during some medical procedure. Neither State statutes nor the common law appear to have provided the patient with clear ownership rights in tissue removed during diagnosis or treatment.

For example, a California statute requires that:

> . . . recognizable anatomical parts, human waste, anatomical human remains, or infectious wastes following conclusion of scientific use shall be disposed of by treatment, incineration, or any other method determined by the State [Health] Department to protect the public health and safety (22).

While this statute does not foreclose the patient from having a limited property right in the anatomical parts that were amenable to use in scientific research, neither does it help a patient meet the burden of proving a clear property right in excised tissue (106). In a State where a statute or regulation forbids possession of tissue taken during treatment except for use in scientific research, a patient would probably have a difficult time in showing entitlement to immediate possession of the chattel.

If a right to possess tissue exists, this right could be argued to apply to all tissue removals, not just tissues that later prove to be of commercial value. If this were true, any bodily material disposed of by a physician could potentially present a claim for conversion. The broad scope of acts amenable to a conversion claim would have potentially large consequences because bodily tissues are routinely discarded by physicians. The interference with the patient's bodily material would not appear to be different whether tissue is thrown away after analysis or the researchers deny that the patient/plaintiff has an ownership interest in a bioengineered product. In both situations, the patient loses control over the tissue once it leaves the body. Thus it may be necessary for a patient/plaintiff to articulate criteria that would restrict the applicability of the conversion doctrine so that it would not apply to all human tissue that is tested by a researcher.

One such distinction may involve the type of tissue. Some substances, such as urine, feces, saliva, and sweat, are byproducts of life that are naturally exuded by the body. Because these substances are routinely discarded by all humans, an individual's claim of a property interest in such substances may be regarded as attenuated due to abandonment (103). Perhaps a patient's claim would be strengthened if the tissue was one that was purposefully removed during a surgical procedure to which the patient had consented, and not simply as part of an ongoing, natural process of secretion or excretion. Some researchers have argued, however, that any deliberately excised diseased tissue is within the public domain once it has been examined by a surgical pathologist (103).

Whether a meaningful distinction can be drawn based on the mechanism by which the tissue is removed from the patient is not entirely clear. Neither case law nor statutes provide any definite answer. Nevertheless, it does appear that the strength of a "lack of possession" defense in a conversion suit may be affected by whether the tissue used in the research is naturally and repeatedly discarded, or is surgically excised.

Injury to Plaintiff

In addition to demonstrating a property interest in the tissue, a successful suit for conversion must show that the plaintiff has suffered some injury through interference with the property. One form of injury is a diminution in the availability (and hence the value) of the property to the plaintiff. But "raw" tissues and cells have little pecuniary value in themselves, especially to the typical patient or research subject who is not trained to identify biological characteristics or develop cell lines or cloned gene probes. Arguably, tumor cells and other diseased tissue have a negative value, so a patient who is "deprived" of these biologicals may typically experience an increase in his physical, psychological, and financial wellbeing. In addition, a researcher's patent on a cell line, recombinant DNA clone, or hybridoma does not reduce the source's right to engage in research on his own (or to employ another scientist) using a similar cell. Since a patent is granted only to that which makes an invention new and unique, using raw material in a patented invention does not prohibit others from using the same raw material in a different way.

Frequently, researchers will create a subculture from an existing cell line (i.e., take a sample of an existing culture and grow this smaller sample separately) and will conduct tests on this subculture. In the meantime, the cells in the original sample may reproduce themselves so that total size of the orignial sample is unaffected. The period of time when the total amount of the cell population is "diminished" is dependent on the rate of cell division. The removal of a subculture of the cell line that is replaced by growing cells may not be regarded by a court as being inconsistent with the patient/plaintiff's property rights in the original culture.

This argument may derive support from a case decided by a Federal appellate court, *Pearson* v. *Dodd* (74). In that case, reporters had obtained possession of photocopies of papers owned by a senator. The papers had been furtively "removed from the files at night, photocopied, and returned to the file undamaged before office operations resumed in the morning." The court found that these actions had not substantially deprived the senator of the utility of his records. Because the plaintiff was not significantly deprived of his property, or its value, the court found that conversion had not taken place.

In a situation where the amount of cultured tissue is limited by the physical environment, and not by time, a researcher possibly could draw on this photocopying case in defending against a claim of conversion (32). When an original manuscript is taken, copied by an outside agent, and replaced, there is no conversion; the same reasoning could apply when a portion of an original culture is taken but naturally replaced by the fecundity of the remaining original material. Either way, the value of the original substance does not appear to have diminished, and the ability of the person who provided the original material to exercise dominion and control over the property probably has not been substantially impaired.

This line of defense, however, probably would not rebut the plaintiff's claim to ownership of the original culture. That is, while the researcher's use of the **subculture** may not have interfered with the patient's exercise of control over property, to exclude the patient from exercising control over the entire **culture** could constitute conversion.

Researchers might attempt to draw a different analogy from the photocopying case. Frequently, surgery is not successful in removing from the patient's body the entire tumor or all pathogenic cells. In this situation, additional cultures could be obtained by removing some of the cells remaining in the body. Accordingly, a researcher could argue that use of the initial culture did not deprive the patient of any property because the culture could readily be duplicated by using cells still within the patient's body. Items that are readily replaceable may be the basis for only a very limited financial recovery by the plaintiff in a conversion suit (107).

This argument, however, may not afford complete protection for the researcher. In some instances, the treatment might eradicate the sample, or make it very difficult to locate additional cells. Moreover, a new sample of the diseased tissue *in vivo* may not be easily accessible. Often, the tumor can only be reached through invasive treatment of the patient. A patient probably would not be barred from claiming conversion on the ground that a replacement culture can be established if the patient must undergo surgery for that new culture to be developed.

Abandonment

The courts have consistently ruled that abandonment of a person's property is a complete defense in any suit alleging conversion. This principle applies to all property, including organic material (28).

In a recent Louisiana case that may be analogous, the plaintiff owned a 130-year-old tree whose limbs extended over a neighbor's house. After a tree surgeon removed these overhanging limbs at the neighbor's request, the landowner sued the tree surgeon for conversion for not having chopped the limbs into firewood. The court ruled in favor of the tree surgeon, finding that he had given the landowner access to the branches. Since the landowner had not exercised any control over the excised limbs—even though she had the opportunity to do so—she could not assert a right to the limbs. The court further supported its conclusion by citing evidence that the landowner had given permission to the tree surgeon to prune the limbs without ever mentioning her desire to keep the excised limbs (11). Although arising in an entirely different factual setting, another case suggests that an individual who takes no affirmative steps to ensure a possessory interest in tissue removed during treatment will encounter difficulties in subsequently asserting any claim to that tissue (12).

Abandonment, if proven by the defendant, precludes a claim of conversion. Whether abandonment of biological materials has occurred, however, can only be decided by looking at the facts in each individual case. The defendant must show "an intention to abandon or relinquish accompanied by some act or omission to act by which such an intention is manifested" (83).

Res Nullius

Another defense that a researcher might assert is **res nullius**, which means things that are not owned (90). The res nullius category included islands newly risen from the sea and wild animals. Under common law, for instance, a distinction was drawn between domestic and wild animals. Domestic animals could be acquired and held as property just like inanimate articles, but wild animals could only be the subject of a qualified property right. Initially, wild animals were common property. The owner of land had the right to take wild animals found on his land, but this right was lost when the animals escaped from the land. The right was mainly of significance in disputes between landowners and poachers (17).

The main way of acquiring rights in wild animals was to lawfully domesticate or confine them. Mere pursuit of a hunted animal was insufficient. If the wild animal escaped, moreover, it could lawfully be seized by others unless they had perpetuated the escape or unless the animal had been domesticated to the point that it probably had an intention to return.

It could be argued the patient and his tissues stand in a relationship similar to that between a landowner and wild animals on his land. If tissues were removed without consent, the wrongful possessor would be like a poacher of wild animals, and would have rights inferior to those of the patient. If, however, the tissues were removed without the removal itself being wrongful, their status would be that of wild animals in a state of nature and the possessor could attempt to exercise dominion over them. Not having exercised dominion or control over the tissues, the patient's rights therein would be like those of a landowner who had made no attempt to capture wild animals passing over his land. The argument seems strongest in the case of tumors because these are not normal, healthy parts of the body. A defendant/researcher could contend that it was he, not the patient, who isolated and cultured the abnormal bodily constituents and thereby reduced them to "possession."

This defense, however, is subject to the counterargument that the physician has a **fiduciary**

duty to the patient, that is, a duty to act in the patient's best interest. This common law duty is imposed because of a patient's emotional vulnerability as well as his reliance on the physician's specialized knowledge. Since the physician's primary duty is to the patient, the exploitation of specimens without the patient's knowledge or consent arguably constitutes a conflict of interest. Furthermore, since property entrusted to a fiduciary remains the property of the original owner, a patient could claim that any research performed without the patient's consent is required to be for the patient's own benefit. Thus, a patient might claim that the transformation of the tumor from res nullius to a living substance now under control was achieved pursuant to a relationship from which the patient should derive the principle benefit. This argument probably could not be made by volunteer research subjects because their participation in providing cells is not for personal benefit.

Law of Accession

Although tissue is a valuable starting point, substantial modifications ordinarily must take place before a commercially valuable product is created. For example, the researcher might take the patient's cellular material, subject it to mutation-causing agents, and then select those mutated cells that show a desirable trait. The biological material may be combined with material obtained from an entirely independent source. The researcher might, for instance, develop a patient's cells into an immortal cell line and then fuse this cell line with the lymphocyte cell of another patient to yield an entirely new hybridoma cell line.

When a product combines biological material obtained from more than one source, or where the biological material has been significantly modified, the legal doctrine of **accession** may be helpful in analyzing ownership issues. The doctrine of accession is derived from the civil law of continental Europe, not Anglo-American common law. It has, however, been invoked by American courts.

Accession is the principle by which the owner of property becomes entitled to all which it produces, and to all that is united or added to it, either naturally or artificially (i.e., by the labor or skill of another), even where such addition extends to a change of form or materials. Under this principle, the possessor of property becomes entitled to it, rather than the original owner, where the addition made by skill and labor is of greater value than the original property, or where the change is so great as to render it impossible to restore it to its original shape (92).

Accession may provide a useful analytical framework for property ownership disputes involving hybridomas and other substantially modified bioengineered products. If the labor of the researcher is regarded as of paramount importance, then title should vest with the researcher. However, if the efforts of the researcher are considered of lesser importance, then the major contributor to the finished product is the patient or research subject. This might be particularly true if the patient had supplied a very rare type of cell. The limited availability of the raw biological material might then be said to enhance the value of the patient's contribution—even if involuntary—vis-a-vis the labors of the researcher.

Cases Involving Crops

A specialized subset of accession cases may have some relevance. Under Roman law, seeds, plants, and trees acceded to the land. Once in the soil, these botanic materials became the property of the owner of the land, regardless of how they were planted or who did the planting (90). As long as the crops remained in the ground, ownership resided with the landowner. For crops that had been removed from the soil, ownership depended on whether they were **fructus naturales** or **fructus industriales**. The former were generally perennials, such as trees, shrubs, and grasses; the latter were usually annuals, such as wheat, corn, rye, and potatoes. Severed fructus industriales crops were owned by the gardener, while severed fructus naturales crops belonged to the landowner. This distinction arose because of the relative amounts of human inputs: in fructus industriales, much effort was expended, while fructus naturales were much less labor-intensive (27,56).

This test would appear to favor the researcher over the patient. Cells taken from the individual can be analogized to a severed crop. To maintain these cells requires considerable effort and energy; they would not thrive if left untended. Therefore, a researcher could plausibly assert that a cell culture is a fructus industriale, not a fructus naturales. Thus, the cells (the severed crop) should belong to the researcher (the cultivator).

Specification

Another variation on the Roman doctrine of accession provides a conceptually helpful tool. Known as **specification**, this doctrine governs situations in which a second person fashions an entirely new product out of materials belonging to another. If specification is applicable, the person who engineers the transformation, not the person whose materials are used, owns the final product. In determining whether specification has occurred, courts look to the uses, values, and common names of the starting material and finished product.

Specification might provide a basis for analyzing many of the factual situations that arise in biotechnology. For example, a researcher might take a blood sample of little commercial value and through mutation and careful selection develop a commercially valuable new cell line. In such a situation, the researcher could assert that specification has taken place because the original cell cannot be recovered from the genetically modified culture (103).

Judicial precedents will be of little help in applying the specification doctrine to modern circumstances. The case law is generally quite old and often inconsistent. While one court has held that grass that is cut and made into hay is not covered by specification (5), another court held that specification vested ownership in the person who had fired the bricks and not the person who had owned the clay (58).

REMEDIES

If the supplier of human tissues and cells prevailed in a lawsuit concerning ownership of a biological product by virtue of cell or tissue ownership, the court would then have to devise a remedy. Unless title has passed through the doctrine of accession, an original owner would be entitled to recover the original property (or its cash value) from the person who had converted the property.

Restoration of ownership, however, does not always occur when property has been disturbed. In a recent case, for example, the plaintiff bought a $2,000 movable home, placed it on cement block, and then left the home for 2 years. In the intervening period, the defendant spent $18,000 to improve the house. The court refused to award the plaintiff the house, saying that this would result in "unjust enrichment," particularly since the plaintiff had virtually abandoned the building (89). This situation could be compared to a patient who asserts ownership of a bioengineered product that had acquired its substantial value only after several years of research and development efforts.

More commonly, a plaintiff alleging conversion will seek monetary damages. In a conversion suit, the plaintiff's damages will ordinarily be the fair market value of the property at the time of conversion (93,105). Usually, providing the owner with that sum should restore the owner to the financial position enjoyed before the conversion.

It may not be entirely clear, however, when the conversion of a biological substance actually occurred. The plaintiff would probably assert that value should be measured at the time when the cell line or gene probe was developed or even later. The researcher, in contrast, would assert that value should be determined earlier, either at the time the tissues or cells were still within the patient's body (when the patient still had physical possession), or after excision but before development. Neither time would be likely to yield a significant damage award for the patient. The tissues or cells would seem to have little value while still in the patient's body or immediately after removal.

Nor is it clear that the tissues or cells would have much value once developed. The great majority of cultures and cloned genes are of no commercial value—only a small fraction are ever patented and only a fraction of patents are licensed (103). Thus, even if the moment of culturing was the appropriate time point, the patient would have to rely on the latent, potential value of the cells—not the immediate utility of the culture—to recover more than a nominal sum (108). However, there may be certain types of tissues or cells which, through rarity or immediately apparent special properties, would have some ascertainable market value once they were cultured (51).

Case law does not provide much direct authority concerning the point in time that should be used to compute damages. Nineteenth century British cases involving the conversion of coal by secretly removing it from a mine do tend to support choosing an earlier point. Cited with approval by the U.S. Supreme Court, these cases hold that the measure of damages is "the value of the coal as it was in the mine before it was distributed, and not its value when dug out and delivered at the mouth of the mine" (38). If this is analogized to a biological materials case, the appropriate point is when the cells are still in the patient. If so, the monetary harm to the patient probably would be trivial. In addition, not all patient tissue is unique or rare. If a bioengineered product is based on tissue with a relatively common trait, the market value of the tissue might be nil, because some biological materials are available at little or no cost from numerous sources.

Nevertheless, while the general rule is that damages are determined at the time of conversion, this rule has numerous exceptions. For example, courts have held that under certain circumstances the plaintiff could recover the highest value of a converted crop at any time between the date of conversion and the date of trial (42,47). Similarly, an individual ordered to leave the land on which he was growing crops was awarded the money that he would have received had the crops matured, not the value of the crops at the moment of his ejection (79). Because the plaintiff had introduced substantial evidence of what the yield of the crop would have been, the court rejected the defendant's argument that damages should be fixed at the moment of the conversion.

Well-established agricultural doctrine may strengthen the claim of the patient or subject to a larger recovery. Unless the parties agree otherwise, the progeny of animals belong to the mother's owner, in accordance with the maxim **partus sequitur ventrem** ("the birth comes from the womb"). And an owner who was wrongfully deprived of livestock can recover for lost output provided that this loss can be established with sufficient certainty, including eggs from converted chickens (39) and milk from converted heifers (63). These cases would seem to support a patient's claim for the value of the output of a cell line resulting from a wrongfully taken tissue or cell. Assuming that a patient did prevail on the conversion claim (68), the recovery might therefore include not only the value of the cells themselves, but also the value of any cell line and product derived from the cell line.

Variation Among States

State courts vary widely in the degree to which they depart from the strict test of market value at the time of conversion. Thus the amount that a plaintiff could recover for conversion of biological material could depend largely on which State's law applies to the claim.

The differences among the States in computing damage awards is illustrated by a California statute. (California is home to many biotechnology companies.) The basic rule in California is that "the owner of a thing owns also all its products and accessions" (18). Under this law,

> . . . [w]hen things belonging to different owners have been united so as to form a single thing, and cannot be separated without injury, the whole belongs to the owner of the thing which forms the principal part (19).

The legislature recognized the potential difficulty in determining which part was "principal." To give guidance to the courts, the following statute was enacted:

> That part is deemed to be the principal to which the other has been united only for the use, ornament, or completion of the former, unless the latter is the more valuable, and has been united without the knowledge of its owner, who may, in the latter cases, require it to be separated and returned to him, though some injury shall result to the thing to which it has been united (20).

Once the owner of the "principal" part has been ascertained, that person can claim ownership to the entire object. However, the owner must "reimburse the value of the residue to the other owner, or surrender the whole to him" (21). This is a substantial change from the common law approach followed in most jurisdictions.

It is clear that computing damages might be difficult in many biological tissue conversion cases. The problems could be further compounded by the need for the plaintiff to identify with specificity his or her property. It will not be enough for the patient to demonstrate that a cell culture or bioengineered product contains tissues or cells that originated with him or her. The patient also must identify specificially the cells which he or she claims to own (45). For example, if cows are converted and then mingled with another person's herd, the cows' owner must identify his particular cows in order to receive an award of damages (60). Simply showing commingling is not enough to justify a monetary recovery.

This need to establish ownership of discrete articles may not be difficult in some situations. Typically, considerable efforts are expended to maintain the purity of a cell line; biological material from another source is ordinarily excluded from a cell culture. Thus in many cases, it would not be difficult to trace to a single source the original material used to make a cell line. When this separate existence is not maintained, however, the plaintiff may have the difficult task of segregating the tissue or cells which he or she originated from those coming from another source.

Moreover, this need to identify specific property may be a barrier to recovery in cases involving anonymous or unidentifiable sources. Researchers frequently test tissues without knowing the source of the material (103). If a patient suspected that his or her tissue had been used to generate a bioengineered product, the individual would need to trace the product back to the tissue originally provided. This could be quite difficult where material has been pooled or where full documentation of tissue source has not been maintained by the research facility.

Third-Party Liability

Good faith of the defendant is generally irrelevant to the merits of the claim in a conversion suit and the person whose property has been converted can prevail, regardless of whether the defendant acted inadvertently (91). The intent of the defendant may, however, affect the damages. Some courts have held that where the acts are willful, the defendant must reimburse the lawful owner for the full value of the property even if the defendant had enhanced the value of the property through labor or materials (75).

Because good faith is not a defense, third parties who unknowingly participated in the conversion may be held liable to the plaintiff (84). Thus an auctioneer who unwittingly sold property that had been converted by a third party has been held liable to the true owner of the property (91). This principle could have important applications for the biotechnology industry. If good faith is not a defense to possession of a bioengineered product derived from a patient's tissue, then innocent purchasers of the product are potentially liable to the patient; similarly, licensees using the product might also be at risk of suit.

SUMMARY AND CONCLUSIONS

U.S. law has long protected people from those who would harm them physically or who would deprive them of full enjoyment of their property. The common law classifies many injuries to persons (which are analyzed under tort law principles) or injuries to property (which generally are within the domain of property law). Congress and State legislatures have enacted a variety of statutes to codify, modify, and overrule the common law.

No area of existing law definitely sets forth the rights held by an individual who provides tissues and cells to an academic or commercial researcher. Because neither judicial precedents nor statutes directly address the questions raised by the use of tissues and cells in research, courts must handle emerging legal questions by using principles and precedents developed for other circumstances. In reasoning by analogy, courts can draw upon possible sources of rights that are outlined in this chapter.

Patent law has direct application to biotechnology research and development. Although patent law does provide inventors with a personal property right in the invention, it does not provide inventors or their sources with property rights in the original, unimproved tissues and cells.

The **law of cadavers and autopsies** provides a historical context for considering the property and quasi-property rights in human tissue. Although property law concepts have been useful in this area, the tort of intentional infliction of emotional distress has been developing as a more appealing theoretical basis for a legal claim based on unauthorized retention of body parts and other forms of wrongful conduct. Today, cases concerning wrongful acts toward a dead body are generally treated as tort cases rather than property disputes.

The **law of organ transplantation** is relevant because it shows congressional intent banning sales of certain human organs. The **law of blood and semen sales** is an area where regulation has been minimal. This area of law does open up the question of whether the sale of replenishing tissues and cells constitutes the sale of services rather than the sale of a commodity. If such sales are treated as the sale of commodities, then Uniform Commercial Code warranties would apply to the merchantability and fitness of such products. In addition, State sales taxes would apply. Although State law generally characterizes such transfers as the sale of commodities, such characterization has not been applied consistently.

The **law of copyright** will not provide a legal remedy for the provider of human biological material unless it can be shown that the source of such material is an author of such material. The **law of trade secrets** provides protection, either by contract or through statute, against the disclosure of certain information. A sample of human tissues and cells is not itself a trade secret but may be characterized as a tangible article representing an intangible trade secret. Still, unless the patient contemplated, at the time of transfer, that the excised tissues or cells had commercial value, it would be difficult to argue that the biological material represented a "trade secret" of the patient.

The **law of conversion and trespass to chattel** may provide tort protection for sources of human tissues and cells where it can be shown that there was intentional interference with personal property. Because tort law is determined primarily by State law, significant variation in the conversion doctrine exists from State to State. The **law of accession**, whereby the owner of property becomes entitled to all it produces, may be helpful in analyzing issues related to ownership of tissues and cells, particularly where the analysis hinges on the comparative value of the raw material provided by the source and the labor expended by the recipient of the material.

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107. *Williams* v. *Board of Education of Clinton Community Unit School District No. 15*, 367 N.E.2d 549 (Ill. App. 1977).
108. *Wolk* v. Nichols, 572 P.2d 1190 (Ariz. 1977).

Chapter 6

Informed Consent and Disclosure

"Every human being of adult years and sound mind has a right to determine what shall be done with his own body."

—*Scholendorff* v. *Society of New York Hospital,*
105 N.E. 92, 93 (1914)

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Chapter 6

Informed Consent and Disclosure

Communication is as important in research as in other professional endeavors. The communication between a physician or researcher and a patient or research subject will vary based on the situation faced by the parties involved. A physician who is removing a tumor from a patient is likely to focus on several issues that differ from those faced by a researcher who is obtaining blood samples from healthy donors for a clinical research trial. Although the dynamics of these two situations differ, an informed consent based on the communication of optimal information remains the desired result.

Consent must generally be obtained from patients and research subjects prior to specimen removal for treatment or experimentation. **Informed consent** refers to a person's agreement to allow the activity to happen, based on full disclosure of the facts needed to make a decision intelligently. Informed consent has several components: disclosure, comprehension, voluntariness, competence, and consent (11). Consent is a process, not a form. The process represents a two-way flow of information between caregiver and patient about the risks and benefits of treatment, leading to an agreement and course of action.

Once there has been a sufficient exchange of information by both parties, and assuming that the prerequisites of legal and mental capacity and voluntariness are in place, the patient is in a position to make an informed and voluntary choice. After a choice of treatment is made and the clinician agrees to carry it out, the consent process is usually complete. The practitioner may then perform the procedures that have been authorized by the patient.

Although the consent process is completed prior to undertaking medical treatment, subsequent diagnostic or therapeutic measures can call for changes in the treatment plan originally agreed to by the physician and the patient. This situation requires new disclosures of pertinent information, a continuing dialog and exchange of information, and a new or modified authorization for treatment.

Health facilities, legislation, or regulations may require a written, signed consent. Some type of written record of the consent process is often necessary to satisfy requirements regarding the quality of treatment, insurance claims, and legal defense. A consent form cannot replace the dialog between the clinician and patient; its proper role is to document that an exchange of information has taken place.

In any discussion of informed consent, it must be realized that many problems that arise can only be settled on a case-by-case basis. The parties involved often enter the consent process equipped with varying degrees of comprehension, competence, and voluntariness of action. This chapter will discuss these problems, as well as investigate the protections available to research subjects and patients.

CONSENT REQUIREMENTS FOR MEDICAL TREATMENT AND HUMAN RESEARCH

Consent requirements take many forms and are based on different principles. Professional medical societies have traditions concerning information exchange with patients. Other requirements emerge from common law, while others are based on State or Federal laws and regulations.

Common Law Consent for Medical Treatment

Common law has developed two different theories of consent. The traditional view, based on the law of battery, holds that unauthorized treatment is actionable as an intentional tort (3). As such, there is no need to prove actual harm to the patient. Although the traditional view is followed in some jurisdictions, it is now well-recognized in common law that the law of battery is generally inadequate to deal with most contemporary consent issues. Patients who claim they received inadequate information about a procedure are not in a position to say that treatment was not authorized. Unless the patient can demonstrate fraud, misrepresentation, or breach of contract, there is no recourse.

The common law in some States has recognized this problem and a new theory of consent law has emerged. Based on the law of negligence, a patient can claim that the consent was invalid because the authorization was based on inadequate disclosure of information. There is no need to prove that the defendant had intentionally tried to harm or deceive the patient. Rather, based on the law of negligence the plaintiff must prove:

- the appropriate standard of disclosure;
- that a breach of that standard took place;
- that as a reasonably foreseeable consequence of this breach, the patient was harmed; and
- that had the patient been properly informed, consent to the procedure would have been withheld (24).

Important elements also include the voluntariness of consent, mental capacity, legal capability, scope of disclosure of information, and exceptions to the general rules for consent.

State Statutory Requirements for Medical Treatment

Several States have enacted so-called "consent to treatment" legislation. The impetus for many of these laws was the malpractice crisis of the 1970s. Many State legislatures also have passed malpractice reform laws, including provisions governing consent lawsuits (8) and the requirements for a valid consent (33). The negligence theory of consent has been given legislative recognition (27), and in some instances the right to bring consent actions on the theory of assault or battery has been removed.

Much of the State legislation concerning informed consent deals with setting requirements for information disclosure. These laws also contain the permissible grounds for not disclosing information to patients. Nondisclosure provisions are often found in statutes that delineate the elements necessary for a consent lawsuit or that specify valid defenses to consent actions. Medicolegal emergencies (13,15), therapeutic privilege (2,28), and requests by patients not to be informed (9,29) are examples of legislative exceptions to the requirements for a valid consent.

Federal Consent Requirements for Human Research

Following World War II, the subject of human research generated much international, Federal, and State discussion. This produced a wide variety of pronouncements (25), guidelines (10), statutes (20,30), and regulations (45 CFR 46, 21 CFR 50) governing human research.

There are two main bodies of Federal regulations governing human research. Promulgated by the Department of Health and Human Services (DHHS) and the Food and Drug Administration (FDA), the regulations detail the elements necessary for informed consent to research and the documentation of that authorization. The DHHS regulations govern research conducted or funded by the Department, including the National Institutes of Health (NIH) (45 CFR 46). The FDA regulations govern clinical investigations that support applications for research or marketing permits for products such as drugs, food additives, biological products, and medical devices (21 CFR 50).

The DHHS regulations have been recognized as being the primary Federal requirements governing the protection of human research subjects. The Interagency Human Subjects Coordinating Committee, which has representatives of 17 Federal agencies, has proposed that the DHHS regulations serve as a model policy for all Federal departments and agencies (51 FR 20204).

As with the requirements for consent found in the traditional treatment context, the DHHS regulations make it clear that consent to research must be obtained from the subject or his legal representative in circumstances that minimize the prospect of coercion or undue influence (45 CFR 46.116). The regulations specifically address issues such as confidentiality, compensation for research-related injuries, the right to withdraw from research without incurring a penalty or loss of rights, and optional disclosure requirements that can be imposed.

The regulations are quite specific in terms of consent documentation (45 CFR 46.117). In most instances, a written, signed consent is required prior to initiating research. The regulations recognize two types of consent documents, the so-called long form and the short form. The long form encompasses all the consent elements required under the Federal regulations. The short form indicates that the subject or the subject's legally authorized representative has been given a verbal account of the required information. The form must be signed by the research subject or representative. The subject or representative must also be given a written summary of the oral explanation approved by the Institutional Review Board (IRB). For such a consent to be valid, the verbal disclosure must be witnessed by another person who, along with the subject or representative, must sign the short-form consent document. The person who obtains the authorization must also sign the short-form consent.

In specific situations, the DHHS regulations provide that consent requirements can be waived. Waiver can occur when the IRB determines that:

- there is no more than a minimal risk to subjects;
- the waiver will not have an adverse impact on the rights and welfare of subjects;
- without the waiver, it would not be practical to carry out the research; and
- under appropriate circumstances, additional details will be given to subjects following their participation in the research project (45 CFR 46.116(d)).

Under FDA regulations, exceptions to general consent requirements are allowed when it is not feasible to secure an authorization prior to using the test article or to preserve the life of the research subject (21 CFR 50.23). However, there is a general prohibition on using exculpatory language to release the investigator, institution, or sponsor from liability for negligence (45 CFR 46.116; 21 CFR 50.20).

Aside from its general consent regulations, DHHS has special provisions governing research using fetuses, pregnant women, and human in vitro fertilization (45 CFR 46.201-46.211); prisoners (45 CFR 46.301-46.306); and children (45 CFR 46.401-46.409).

State Consent Requirements for Human Research

California, New York, and Virginia have legislated specific consent requirements for human research (5,18,31). Each of these State laws makes it clear, however, that research subject to Federal regulatory requirements is exempt from State provisions (7,21,32). Other States have less detailed legislative provisions regarding human research. These laws, frequently codified under State nursing home or long-term care statutes, are usually part of patients' rights legislation and simply indicate that informed consent is required for persons enrolled in human research (16,17). Other provisions indicate that individuals may decline to participate in human research (4,23).

The fact that only a few States have enacted detailed legislation governing consent and human research, even though Federal regulations apply directly only to federally sponsored research and clinical investigations, may reflect a belief that the States are not equipped to regulate or monitor human research. It could also be interpreted to mean that State legislators do not believe the subject is so pressing as to require legislative initiatives. Another possible explanation is that Federal regulations are so detailed—and that IRBs tend to judge all research according to federally mandated standards even if not federally sponsored—that there is little need for further legal controls at the State level.

Although human research has not generated much legislative response at the State level, the laws that have been enacted convey a rather clear message regarding the well being and needs of research subjects. These State laws require a **voluntary** authorization prior to participation from either a competent research subject or, in some instances, the subject's legal representative, with a considerable emphasis on a **written** informed consent.

Institutional Review Boards

DHHS regulations require institutions performing human subject research to create and use Institutional Review Boards to review proposed research projects for compliance with detailed human subject research regulations if the research is funded by the Department or its constituent agencies (45 CFR 46.103(b)).

Since NIH is the primary source of funding for biomedical research undertaken at medical schools, graduate science programs, and research hospitals, the regulations appear at first glance to cover human specimen research. However, research involving pathological or diagnostic specimens is exempt if the specimens are publicly available (for instance, from a tissue culture depository) or if the information is recorded by the investigator in such a manner that subjects cannot be identified (46 CFR 101(b)(5)).

OTA commissioned a survey of the IRBs serving 23 medical institutions to determine the practices of these institutions with respect to informed consent for specimen procurement and research. Of 22 responding institutions, none reported any special cases or problems arising with respect to using human biological materials. The survey suggests that IRBs hold researchers to more stringent ethical standards than are required by law. All of the IRBs reported that the same standards are used to review and justify all research projects in their institutions, regardless of the source of funding, even though compliance is only mandated for federally funded projects.

Voluntariness of Consent

Voluntariness of consent is an important consideration in treatment and research. For a consent to be voluntary, the authorization must be given freely. There should be no suggestion of undue influence or coercion. In reality, it is hard to insulate the patient or research subject from the most subtle—let alone sometimes overt—institutional and social pressures.

Patients may agree to treatment to avoid confrontation or to satisfy some personal, family, or social objective. Indeed, some patients suffering from serious medical problems may not be capable of a totally voluntary consent if the alternative to a proposed procedure is the prospect of lingering illness or death.

When the prospect of commercial gain is introduced into the research setting, concern arises about the voluntariness of consent. Will subjects be unduly influenced by the knowledge of possible commercial gain? Will researchers unduly influence or coerce subjects who are the source of marketable, biological material? If these are genuine concerns, what steps can be taken to minimize the prospect of a less than voluntary consent?

Factors Influencing Voluntariness of Consent

A variety of factors can influence the voluntariness of consent to participate in research. Three of these are:

- satisfying psychological, emotional, or medical needs;
- desire to please others; and
- the prospect of financial gain.

There is no doubt that for many subjects, participation in human research satisfies some psychological, emotional, or medical need. The psychological or emotional impetus for taking part in a study may not be clearly defined, but affliction with or recovery from a serious illness, or the loss of a loved one, are sometimes rationales for research participation. Taking part in a study sometimes satisfies a need for attention. In most instances, it is not troublesome that a subject participates in a research project to satisfy an emotional or psychological need. However, when researchers who are aware of this inner need exploit it to gain consent, then voluntariness becomes an issue. Controlling this problem can be difficult, particularly because the undue influence may be quite subtle yet very effective. IRBs and researchers alike must be diligent to safeguard against this problem.

The desire to please others can also pressure people into participating in research. This is particularly of concern among those persons who see their participation as a way to gain the favor of someone in authority or for whom they have considerable respect. Considerable doubt can be cast on the ability of subjects in a dependent relationship to achieve a voluntary consent. Prisoners and those in long-term care facilities typify such potential subjects. Such concerns are embodied in the DHHS regulations dealing with prisoners as research subjects (45 CFR 46.301-46.306). However, this problem can also manifest itself in other dependent groups (e.g., children, the elderly).

The prospect of financial gain may also influence a subject's decision to give consent. If a researcher places considerable emphasis on the prospect for financial gain with impoverished research subjects, such information may be an undue influence. Even compensation for expenses and inconvenience could provide some impetus to participate. The question remains whether these influences are inherently bad, or if not, are so strong as to be unwelcome. If so, safeguards could be designed to minimize their effect.

Legal Dynamics of the Physician/Researcher and Patient/Research Subject Relationship

Like the relationship between a physician and a patient, the physician/researcher liaison with a patient/research subject is one of a fiduciary trust. The physician/researcher owes a special duty of care to patient/research subjects and must not act in a way that jeopardizes the rights and welfare of participants. This includes obtaining authorizations for participation in research in a manner that is free of undue influence and based on a fair and comprehensive disclosure of information.

The danger of undue influence is as real in the research setting as it is in the medical treatment context. The results can be far worse in the treatment context, however, where subjects who agree to unnecessary procedures or tests must pay health facilities or clinicians. Moreover, in the treatment setting the institutional and IRB safeguards for human subjects are often not present.

For some physician/researchers, the prospect of **commercial gain** can represent a conflict of interest. Two distinct duties are present: one as a principal investigator and the other as an attending physician to the patient/research subject. The interests of the researcher may be far different from the concerns of the attending physician. The researcher may see the subject as an invaluable source of scientific knowledge or perhaps commercial gain. The physician sees a patient requiring careful diagnostic testing and treatment. When the researcher and attending physician are the same person, the desire for financial gain could overshadow the concern for the well-being of the patient/research subject. Research might be carried out that would ordinarily be avoided and treatment that would usually be conducted might not be pursued.

Commercial gain is not the only motivation for unduly influencing physician/researchers. For some, the potential for **public or scientific recognition** may be more of an impetus to unduly influence subjects than the thought of reaping financial reward. While it may be difficult to discern public or peer recognition as a cause for concern, the potential exists for the physician/researcher to conduct himself/herself in a manner that unduly influences the subject.

It is difficult to determine whether or not undue influence is a serious problem in medical-based human research. If it is, there are limits to what can be done to eliminate it. Educating physician/researchers about the proper means of obtaining consent, monitoring the consent process, requiring consent documentation, and taking appropriate action when discovering instances of undue influence are all practical options. In addition, professional boards can discipline those who have acted improperly.

The ability of research subjects to perceive undue influence should not be discounted. The effect of the consumer movement has spread to health care and patients have become more reluctant to agree to treatment without first being satisfied of the need for and the costs of it. Patient-research subjects, too, are likely to inquire about the purpose, needs, and benefits of studies.

Finally, when enforced properly, the current Federal human research regulations provide a considerable degree of protection against undue influence in the consent process. Full enforcement of current provisions along with proper disclosure of the prospect for commercial gain may therefore be the most practical safeguards against undue influence with respect to human tissues and cells of potential commercial value.

DISCLOSURE REQUIREMENTS

For a consent to be valid, the patient or research subject must be given an adequate amount of information with which to reach a reasoned choice. Perhaps no other aspect of consent has generated more case law and discussion among scholars than the extent of required disclosure of information.

Disclosure requirements can vary in different settings. The following sections consider standards of disclosure in three contexts: disclosure in the medical treatment setting, disclosure in the research setting, and disclosure when potential commercialization of a product is contemplated.

Disclosure Requirements in Medical Treatment

In the United States, there are two schools of thought regarding the disclosure standard in consent to treatment. The traditional view, held by a majority of States, requires disclosure of information that the medical community customarily discloses to patients (24). This standard is based on what physicians view as important, as well as what facts physicians believe patients should know before agreeing to treatment.

A modern trend, adopted by a minority of States, bases disclosure requirements on what a reasonable person in the patient's position would want to know in the same or similar circumstances. Unlike the physician-oriented approach, this standard is based on patient need and recognizes that patients want to take a more active role in their treatment. To this end, patients need information that is material or significant to their decisions regarding recommended care (24).

The patient-need approach involves the patient in making decisions and it compels physicians to communicate with patients. It enlarges the consent process to take into account matters beyond the mechanics of a proposed form of care. The patient-need standard considers the probable impact treatment will have on employment and lifestyle as well as the financial and emotional costs to the patient. State courts are increasingly adopting this view in preference to the physician-based standard.

Both approaches to disclosure would generally include the following information in disclosure to patients:

- the nature and purpose of a diagnostic, medical, or surgical intervention;
- probable, foreseeable risks and benefits associated with the intervention;
- the availability of reasonable, alternative procedures and the probable, foreseeable risks and benefits associated with these optional interventions;
- an explanation of probable complications, discomfort, disability, or disfigurement associated with recommended, as well as optional, interventions; and
- the probable, foreseeable risk(s) associated with foregoing all interventions (24).

Additional disclosure requirements are sometimes needed. For example, it may be argued that patients in teaching hospitals should be informed that students, interns, or residents may take an active role in their health care because this information may be an important consideration for some patients in agreeing to or refusing recommended therapy.

Case law recognizes that certain types of information need not be disclosed. For example, under the patient-oriented standard the clinician need not divulge information regarding:

- risks already known to the patient,
- obvious risks which the patient may be presumed to know,
- remote risks with a very low incidence asso-

ciated with proposed care or testing, and

- risks either unkown to the clinician at the time consent is obtained or that in exercise of reasonable care could not be ascertained (26).

Case law involving the physician-oriented standard does not provide a hard and fast rule for what the doctor need not disclose. This is a matter based principally on the facts and circumstances of each case, taking into account customary practice in the medical community. Should litigation ensue in a case controlled by the physician-oriented viewpoint, expert testimony would likely be required to establish what is the acceptable scope of nondisclosure (24).

Both standards recognize certain exceptions when the need for disclosure is outweighed by other considerations (26). These include medical emergencies, situations where disclosure could be detrimental to the patient's well-being, and instances of legal or mental incapacity. Thus, disclosure of information cannot be considered in a vacuum. Whether clinicians follow either the professional or patient-need standard of disclosure, it is imperative for them to take into account the surrounding facts and circumstances of each case. How this information is interpreted and applied helps to differentiate the two standards for disclosure.

Several State legislatures have set requirements regarding what information needs to be disclosed (2,22,28,33), the types of information that need not be revealed (29,33), and the circumstances in which disclosure need not be made (13,25,33). Remote risks (2) or risks that are commonly known (2,18,29) need not be revealed. Similarly, medicolegal emergencies (13,15,33) and statutory versions of therapeutic privilege (2,9,28) create exemptions from the standard requirement for disclosure of information.

The law is far from settled in the area of disclosure standards and some decisions have sparked controversy. For example, how far must a physician go in making certain that a patient's **refusal** of care is informed (12)? Moreover, does the duty to reveal information about reasonable alternative procedures include mention of those procedures that are more hazardous than the recommended intervention? The Supreme Court of

Box D.—Physicians' and Patients' Views of Informed Consent and Disclosure

The President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research was established by Congress to investigate the ethical and legal implications of the requirements of informed consent to undergo medical procedures. In 1982, the now defunct Commission determined that insufficient data existed concerning physician and public attitudes toward informed consent and commissioned a national survey to investigate the issue of informed consent in therapeutic settings. Interviews were completed with a national sample of 805 physicians and a national cross section of 1,251 adults.[1]

The vast majority of physicians reported that they "always" or "usually" discuss most aspects of condition and treatment with their patients. As might be expected, the proportion of doctors who report disclosing information to their patients is greater than the proportion of the public who report that doctors discuss these matters with them. In most instances, there was a difference of 15 to 25 percentage points between the proportion of doctors who report usually discussing the issue with their patients and the number of patients who report that their doctors usually discuss these matters with them.

Seventy-three percent of the doctors and 44 percent of the patients felt the requirements of informed consent put too much emphasis on disclosure of remote risks.

Physicians demonstrated some confusion about the legal requirements related to informed consent. Only 32 percent of the physicians felt that the legal requirements for obtaining informed consent are clear and explicit.

Although diagnostic blood tests are a significant potential source of human research specimens, only 2 percent of doctors ask their patients to sign written consent forms, while 49 percent of doctors get oral consent and 43 percent get no consent at all.

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[1] President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, *Making Health Care Decisions*, Volume 2: Appendices (Empirical Studies of Informed Consent) (October 1982).

SOURCE: Office of Technology Assessment, 1987.

Connecticut has suggested that "reasonable" alternatives does include description or inclusion of more risky options (14). It remains to be seen whether other courts will adopt that court's definition of a reasonable alternative.

What constitutes an appropriate amount of information disclosed to a patient under the physician-oriented standard may be as hard to discern as "material" or "significant" information under the patient-oriented approach. The courts have evaded setting precise requirements. As a result, more, rather than less, case-law development can be anticipated in this area of consent.

Disclosure in the Research Setting

Federal law requires far more information to be disclosed to obtain valid consent in a research setting than in a therapeutic setting. Under Federal regulations (45 CFR 46.116) and some State statutes (6), all reasonably foreseeable risks and discomforts that subjects might experience must be disclosed.

Risk information is not the only type of information that requires greater elaboration in the research setting. Federal law also mandates disclosure regarding:

- the nature and purpose of the research;
- anticipated length of subject's participation in the study;
- procedures to be followed;
- identification of experimental procedures;
- benefits to the subject or others that may be reasonably anticipated from the study;
- alternative procedures or treatments that may be advantageous to the subject;
- steps to be taken, if any, to maintain confidentiality of records identifying participants;
- whether compensation and treatment are available for injury arising in a study where more than minimal risk is involved;
- if compensation or/for treatment is available, what it consists of, or where additional details may be obtained; and
- who should be contacted if subjects have questions regarding the research or their rights, and the contact person in the event of research-related injury (45 CFR 46.116(a)).

In addition, the researcher must explain that subjects are voluntarily taking part in research and that their refusal to participate will not incur a penalty or loss of benefits to which they are otherwise entitled. Moreover, they must be told that they may withdraw from the study at any time without incurring a penalty or loss of benefits to which they are entitled.

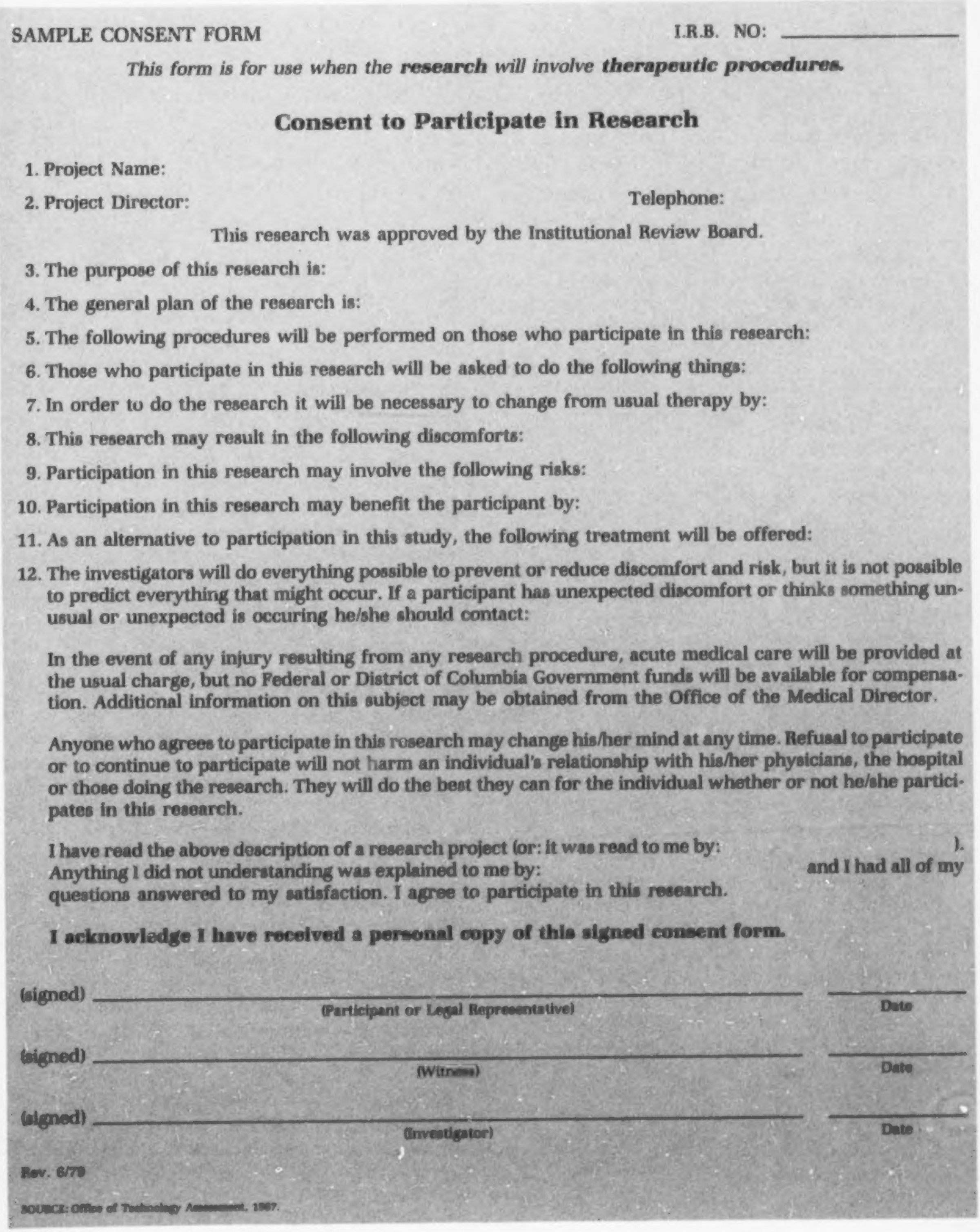
The same States that have detailed statutes on consent and human research have similar disclosure requirements (6,19). However, the Federal regulations are more comprehensive, listing additional information that should be revealed to research subjects if deemed appropriate (45 CFR 116(b)). This may include:

- situations in which the subject's role in the study may be ended by the researcher without regard to the participant's consent,
- other costs to the subject that may result from the research study,
- the consequences of the participant withdrawing from the project and the means for an orderly conclusion to the subject's involvement,
- a statement that significant new findings achieved in the course of the research relating to the subject's willingness to carry on in the study will be provided to the subject, and
- the approximate number of persons taking part in the study.

Although Federal regulations emphasize full and candid disclosure of information, there are circumstances where an IRB may approve practices that alter or exclude some or all of the elements for consent. To do so, the IRB must document that the research involves no more than "minimal risk" to subjects, defined in the regulations as:

> [T]he risks of harm anticipated in the proposed research are not greater, considering probability and magnitude, than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests (45 CFR 46.102(g)).

In addition, the IRB must determine and document that modifying the consent requirements will not have an adverse impact on the rights and welfare of subjects. It must also be shown that



SAMPLE CONSENT FORM I.R.B. NO: ________________

*This form is for use when the **research** will involve **therapeutic procedures.***

Consent to Participate in Research

1. Project Name:
2. Project Director: Telephone:

This research was approved by the Institutional Review Board.

3. The purpose of this research is:
4. The general plan of the research is:
5. The following procedures will be performed on those who participate in this research:
6. Those who participate in this research will be asked to do the following things:
7. In order to do the research it will be necessary to change from usual therapy by:
8. This research may result in the following discomforts:
9. Participation in this research may involve the following risks:
10. Participation in this research may benefit the participant by:
11. As an alternative to participation in this study, the following treatment will be offered:
12. The investigators will do everything possible to prevent or reduce discomfort and risk, but it is not possible to predict everything that might occur. If a participant has unexpected discomfort or thinks something unusual or unexpected is occuring he/she should contact:

In the event of any injury resulting from any research procedure, acute medical care will be provided at the usual charge, but no Federal or District of Columbia Government funds will be available for compensation. Additional information on this subject may be obtained from the Office of the Medical Director.

Anyone who agrees to participate in this research may change his/her mind at any time. Refusal to participate or to continue to participate will not harm an individual's relationship with his/her physicians, the hospital or those doing the research. They will do the best they can for the individual whether or not he/she participates in this research.

I have read the above description of a research project (or: it was read to me by:). Anything I did not understanding was explained to me by: and I had all of my questions answered to my satisfaction. I agree to participate in this research.

I acknowledge I have received a personal copy of this signed consent form.

(signed) ______________________________ __________
(Participant or Legal Representative) Date

(signed) ______________________________ __________
(Witness) Date

(signed) ______________________________ __________
(Investigator) Date

Rev. 6/79

SOURCE: Office of Technology Assessment, 1987.

as a practical matter the study could not be pursued without the consent modification. When appropriate, however, subjects taking part in studies in which consent requirements have been modified must be given relevant information following their participation (45 CFR 46.116(d)).

The need for a detailed disclosure of risk information in the research setting is also found in case law. As a Federal appellate court wrote:

> . . . [F]or a physician to avoid liability by engaging in drastic or experimental treatment, which exceeds the bounds of established medical standards, his patient must always be *fully informed* of the experimental nature of the treatment and of the foreseeable consequences of the treatment (1).

The common-law approach to disclosure in the research setting is pragmatic. The degree of information revealed to a subject will vary from case to case, but some basic principles apply. The greater the probability of risks and the more novel or experimental the procedure, the more detailed should be the information divulged to research subjects. This is an extension of the basic concepts of consent dealing with personal autonomy and the need for sufficient information to reach a reasoned decision about care.

Disclosure Requirements and Commercial Gain

In medical settings, the information disclosed to patients traditionally has focused on the risks and benefits of diagnostic tests or treatment, as well as alternative procedures. In the research context, the disclosure of information has centered on the nature of the study, the involvement of subjects, and any risks involved. However, arguments over the nature of disclosure arise when the prospect of commercial gain becomes an issue.

Arguments Favoring Disclosure Regarding Commercial Gain

Several arguments could be proposed to justify why disclosure of potential commercial gain should be required in the research setting. If the right to decide what will be done to one's own body is to be given full legal recognition, then the prospect of any person achieving commercial gain as the result of any invasive procedure should be disclosed because this information may help a person decide whether or not to take part in the research. While this information may not be pertinent to medical risks and benefits, it can be viewed as a logical extension of the information already required for consent.

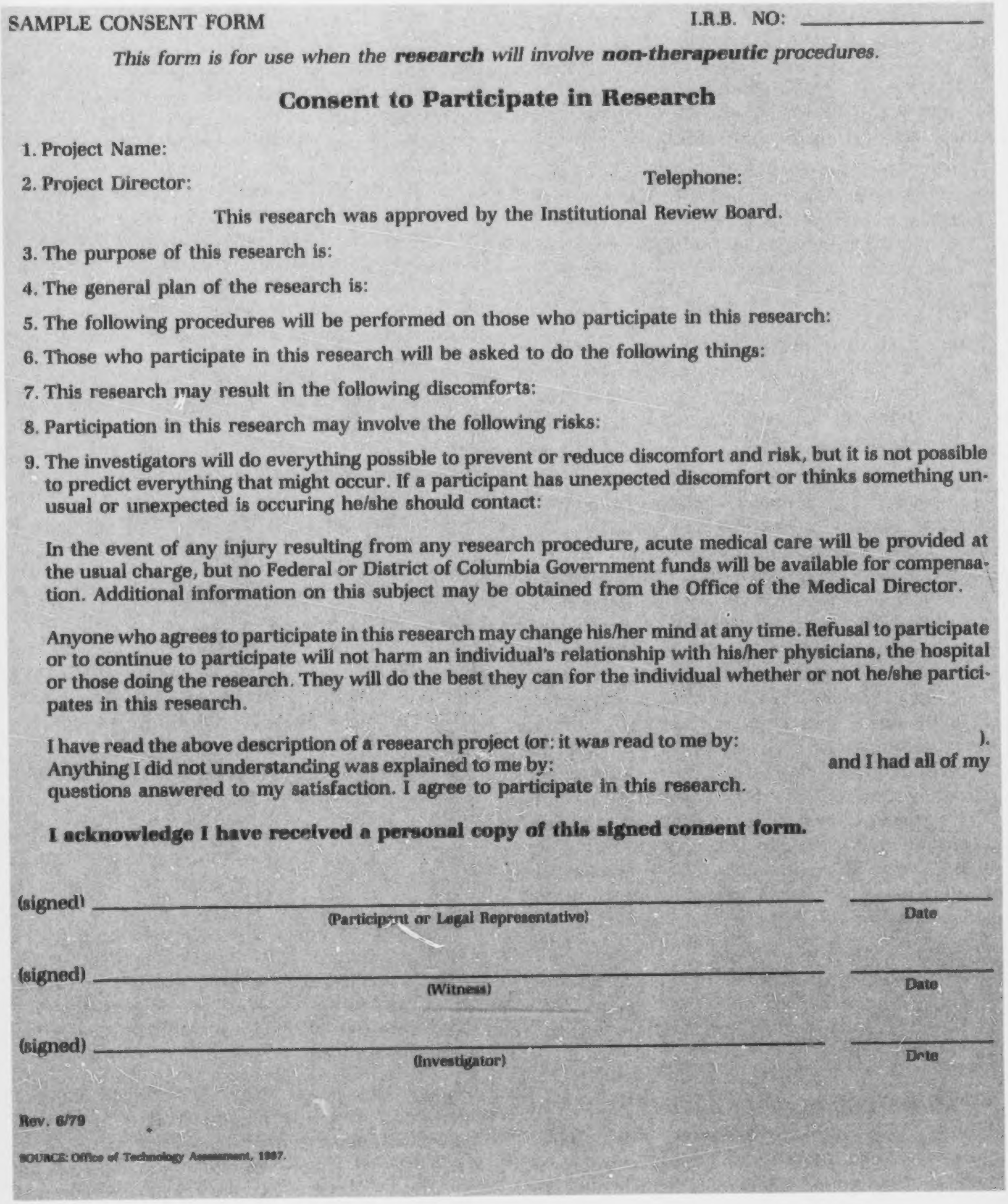
Under current Federal regulations it can also be argued that at some point in the course of research, disclosure of potential commercial gain is required. The regulations require disclosure "when appropriate . . . significant new findings [are] developed during the course of the research which may relate to the subject's willingness to continue participation" (45 CFR 46.116(b)(5)). It can be argued that the discovery in a subject's body of a unique cell line that may be commercially valuable constitutes a significant new finding. This type of information could influence a subject in deciding whether or not to continue his role in the research project. As such, under the regulations it may be the type of additional information that can be required when deemed appropriate by an IRB.

It also can be argued that in a medical treatment context, disclosure of commercial gain should be deemed "material" or "significant" information. Under the patient-need approach to disclosure, this would require that the patient be provided with such information. Since greater disclosure is usually required in a research setting, it would follow that disclosure of potential commercial gain would be required there as well.

Arguments Against Disclosure Regarding Commercial Gain

Arguments can also be made against disclosing the prospect of commercial gain. One argument opposing disclosure, is that the prospect of commercial gain is highly speculative and to bring up the subject in a consent dialog may detract from the more important aspects of the process. This interference may not rise to the level of undue influence, but it could impede subjects from taking an effective role in the consent process.

It can be argued that commercial gain should not be disclosed if it would hamper the subject's



SAMPLE CONSENT FORM I.R.B. NO: ________________

*This form is for use when the **research** will involve **non-therapeutic** procedures.*

Consent to Participate in Research

1. Project Name:
2. Project Director: Telephone:

This research was approved by the Institutional Review Board.

3. The purpose of this research is:
4. The general plan of the research is:
5. The following procedures will be performed on those who participate in this research:
6. Those who participate in this research will be asked to do the following things:
7. This research may result in the following discomforts:
8. Participation in this research may involve the following risks:
9. The investigators will do everything possible to prevent or reduce discomfort and risk, but it is not possible to predict everything that might occur. If a participant has unexpected discomfort or thinks something unusual or unexpected is occuring he/she should contact:

In the event of any injury resulting from any research procedure, acute medical care will be provided at the usual charge, but no Federal or District of Columbia Government funds will be available for compensation. Additional information on this subject may be obtained from the Office of the Medical Director.

Anyone who agrees to participate in this research may change his/her mind at any time. Refusal to participate or to continue to participate will not harm an individual's relationship with his/her physicians, the hospital or those doing the research. They will do the best they can for the individual whether or not he/she participates in this research.

I have read the above description of a research project (or: it was read to me by:). Anything I did not understanding was explained to me by: and I had all of my questions answered to my satisfaction. I agree to participate in this research.

I acknowledge I have received a personal copy of this signed consent form.

(signed) ________________________________ ____________
(Participant or Legal Representative) Date

(signed) ________________________________ ____________
(Witness) Date

(signed) ________________________________ ____________
(Investigator) Date

Rev. 6/79

SOURCE: Office of Technology Assessment, 1987.

ability to reach an informed choice free of undue influence. The prospect of financial security stemming from marketable products derived from human tissues and cells could interfere with some people's ability to reach an informed decision.

Disclosing information regarding commercial gain could jeopardize the health and safety of some subjects, as well as the validity of the research itself. For example, upon learning of the prospect of commercial gain, some potential subjects might be hesitant to relate medical or personal history information that would otherwise disqualify them from the study. This could result in studies generating invalid or skewed data. It could also jeopardize the health and safety of subjects who by their actions expose themselves to unacceptable and unanticipated risks.

Requiring researchers to disclose information about potential commercial gain is arguably inconsistent with their professional responsibility to inform subjects about health-related details. Researchers may not be sufficiently informed themselves to realistically explain the prospect of commercial gain. In fact, the researcher may not even be the physician of record who interacts with the subject. While an investigator may think there is an opportunity to successfully market unique human biological materials or products invented from specimens, in fact there may be little likelihood of this becoming a reality. For researchers to divulge such information could convince subjects to participate in research on the basis of misinformation, unreasonable expectation, or for the sole purpose of financial gain. This would be contrary to the general principles of consent and disclosure.

Finally, full information regarding potential commercial gain may be impossible to convey in many instances since the prospect of such gain is likely to be vague and speculative at the time the sample is obtained.

Standard for Disclosing Commercial Gain

In the medical treatment setting, it is unlikely that a court following the viewpoint of disclosure held by most States would require clinicians to inform patients of the prospect of commercial gain accruing from the use of patients' tissues and cells. Based on a professional disclosure standard, the majority viewpoint is concerned with what the medical community considers necessary information for patients to know in making a treatment decision. Even with the viewpoint held by a minority of States, based on patient need, it is uncertain whether the prospect of commercial gain would be "material" or "significant" to a patient contemplating actual treatment or an invasive diagnostic procedure. It will be up to the courts or State legislatures to decide whether the possibility of commercial gain for any interested party requires disclosure where diagnostic tests or active treatment is contemplated.

In the research setting, where subjects may be enrolled in studies offering little likelihood of direct benefit and where there may be serious known or unknown risks, disclosure of commercial gain may be an important consideration. Such information is likely to be particularly important when the marketing of a product containing human tissues and cells is quite probable. It is a factor that goes to the core of personal autonomy and a subject's determination whether or not to be the source of a commercially viable commodity. It should not be assumed that all persons, upon learning that they carry a unique cell strain or other type of biological material, will agree to its commercial marketing as a developed cell line. Some people may be opposed to such use (see ch. 8).

Safeguards can be developed and put in place that minimize any detrimental impact flowing from disclosure of probable commercial gain, if policymakers, IRBs, or researchers determine that such disclosure is desirable. These include determinations regarding the content and timing of such disclosure and the standard for revealing such information. The standard determines how much information regarding the treatment or research project will be given to the subject.

When the focus shifts to novel or experimental interventions or research, the standard for disclosure is broadened even further. No longer is the standard tied to conventional medical beliefs or the informational needs of a reasonable person. Federal regulations require disclosure of any procedures deemed experimental (45 CFR 46.116(a)(1)) and any foreseeable risks or discomforts stemming from the study (45 CFR 46.116(a)(2)).

The full disclosure requirements found in the research setting may be appropriate for most nontherapeutic or experimental studies. However, when a study focuses on human biological material it may well be asked whether the prospect of commercial gain needs to be disclosed in all nontherapeutic or research settings or if a less stringent standard would suffice?

Questions like these arise because in many instances tissues and cells can be obtained with a minimum of risk to research subjects. In other instances, diseased tissues or cells must be removed from a patient in order to save life or protect health. From a practical point of view, it may be unwise and unnecessary to impose upon all human research projects an additional disclosure requirement regarding possible commercial gain.

This view is reinforced by current Federal regulations. Research involving the collection and study of pathological or diagnostic specimens is specifically exempt from the disclosure regulations if:

> . . . these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects (45 CFR 46.101(b)(5)).

Another Federal provision relates to the authority of IRBs to approve studies in which all of the elements of informed consent are not present (45 CFR 46.116(d)). This may occur when, among other things, studies involve no more than minimal risk and such modifications will not have an adverse impact on the rights or welfare of subjects.

If research involves no more than minimal risk to the patient, and commercial gain is not likely, a blanket requirement to inform subjects about commercial gain may be unnecessary. In such circumstances, the IRB could be empowered to exclude reference to commercial gain.

However, if it is probable that research may yield a commercially significant product derived from a human sample, disclosure may become more necessary. In this instance, the pecuniary and privacy rights of subjects may be compromised if the possibility of commercial gain is not disclosed. Moreover, the welfare of such subjects might be given inadequate attention if the prospect of commercial gain clouds objectivity. When commercial gain is probable, the rights and welfare of subjects may require full disclosure.

The opportunity to identify potentially marketable tissues and cells in research may set a new but limited disclosure standard. Rather than requiring disclosure about commercial gain in all cases, it could be limited to those instances where marketable material is reasonably foreseeable. However, when information is available that is "material" to a subject's decision as well as his rights and welfare, disclosure is imperative. That a subject may garner financial security, experience a loss of privacy, or become the target for commercial ventures as a result of biological substances derived from tissues or cells is arguably "material" or "significant" information. As such, careful consideration should be given to incorporating such a "materiality" disclosure requirement in the human research regulations.

Content of Disclosure Regarding Commercial Gain

The need for a full and frank disclosure of the prospect of commercial gain must be balanced against the potential impact such a revelation may have on the ability of potential subjects to reach reasoned judgments about participating in a study. The content of such a disclosure should be consistent with other information requirements for consent (45 CFR 46.116). This would include:

- the nature and purpose of using human biological material obtained in the course of the research;
- the probable risks associated with obtaining the material;
- the probable benefits flowing from obtaining the material and the probable beneficiaries of these substances or knowledge derived from same;
- the possible commercial gain that may result from developing the biological material in question;
- a description of the method(s) the investigator intends to use to obtain the biological material from research subjects;

- the availability of reasonable, alternative ways of obtaining such material and the probable risks and benefits associated with these alternatives;
- the name and location of persons to be contacted if subjects have any questions or concerns during the course of the study;
- the availability of treatment or compensation for injuries stemming from the study; and
- the right of subjects to withdraw from or to participate in the project without prejudicing their ability to secure treatment to which they are otherwise entitled.

Timing of Disclosure Regarding Commercial Gain

Choosing the correct time to tell a subject or patient of potential commercial gain presents two different concerns. One is that the prospect of commercial gain could unduly influence the subject. The other is whether a researcher has a responsibility to inform subjects whenever new developments alter the original terms on which the consent was based.

On disclosure of possible commercial gain, some subjects may withhold information they believe might make them ineligible as participants. This could result in flawed research results and possibly put the subject and others in the study at serious and unnecessary risk. To overcome this difficulty, potential subjects must be carefully screened to make certain that they meet eligibility criteria. Only then should a full disclosure take place, including the reasonably foreseeable prospect of securing commercial gain.

A second concern relates to the probability of commercial gain discovered subsequent to the participant's entry into the study. The need for full disclosure continues until the conclusion of treatment or research. Indeed, the duty to advise patients or subjects may extend much longer, particularly when individuals are at risk as a result of treatment or research procedures. When significant discoveries are made in the course of research and they alter the basis of the consent, the investigator should reveal this information to subjects. The reasonably foreseeable prospect of commercial gain determined in the course of a research study amounts to a "significant new finding" that may have an impact on the subject's willingness to carry out his role in the project (45 CFR 46.116(b)(5)).

ARE CHANGES NEEDED IN THE CONSENT PROCESS?

The current DHHS regulations contain two provisions that concern research involving human biological material. The first excludes certain types of specimens from the regulatory requirements (45 CFR 46.101(b)(5)) . The second prohibits the use of exculpatory language through which the subject is made to waive or appear to waive any legal right (45 CFR 46.116).

Federal Research Exclusions

The DHHS informed-consent policy applies to virtually all human research funded by the Department. However, an exemption exists for research involving the collection or study of existing data, documents, or pathological or diagnostic specimens if these are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified. Researchers are therefore not obliged to disclose their research or commercial interests to providers of specimens in these instances.

This may pose an ethical problem for some people because researchers might garner commercial reward from work carried out on unknown subjects. From this point of view, it could be argued that the regulations should be amended, either by:

1. prohibiting researchers from reaping financial rewards from such discoveries,
2. requiring the application of informed consent requirements to the collection and use of such specimen material, or
3. disclosing to the subject that a specimen might be used in research that may or may not result in the development of a commercial product.

From a practical point of view, trying to identify the human sources of "existing" specimens would be cumbersome, if not impossible. In addition, more harm than good may be achieved in trying to secure consent because research efforts can be impeded by trying to overprotect patients whose primary interest—diagnosis or treatment—is unrelated to the research.

If the consent process is changed to include a disclosure requirement concerning commercial gain, this disclosure could be limited to those instances where there is a significant probability of commercial gain (i.e., a high probability or certainty of a marketable biological material being extracted) arising from the use of human tissues and cells from an identified research subject. This information would be conveyed during the consent process, when the researcher provided other required details relating to risks, benefits, and alternate treatment options. To overcome the potential for unduly influencing research subjects, researchers should be cautious not to give any more or less emphasis to details regarding commercial gain than is given to other required information.

As with other types of information, disclosures regarding potential commercial gain should be in understandable terminology, with research subjects receiving a full and understandable explanation regarding the human tissues and cells that may be developed by a researcher into a marketable resource, as well as the definition of "commercial gain." Subjects should be given ample opportunity to ask questions and should be given sufficient time to carefully consider whether they want to participate in a study that might result in commercial gain.

While the law of consent is designed to safeguard the rights of the person relating to his or her body, it has its limits. Consent cannot, and arguably should not, prevent researchers from reaping financial reward as the result of research developing tissues and cells collected from another person. It can only assure subjects of a fair level of communication regarding their participation in research. The propriety of researchers achieving financial success from manipulating human specimens in their research is an issue best handled under other legal theories and principles. This may include provisions in research contracts, property law, or perhaps professional disciplinary laws.

Federal Exculpatory Language

The purpose of the DHHS human research regulations is to safeguard the rights and welfare of research subjects. This is particularly apparent in the consent regulations. This approach includes a provision which in part bans the use of exculpatory terms "through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights (45 CFR 46.116).

The intent of this provision is to safeguard subjects and to make certain that they do not wittingly or unwittingly relinquish any legal rights. This concept reinforces the notion of consent as a communication process arising from the physician-patient or researcher/subject relationship. It also reflects the concept of consent as a contractual matter in which parties on both sides should be working from positions of comparable strength. The issue arises, however, as to whether the ban on exculpatory language should be lifted for instances of potential commercial gain.

Some subjects may not want to reap financial benefits as a result of or as a byproduct of their participation in research. This may offend their sense of values and deter them from taking part in studies. Moreover, the prospect of sharing possible financial gain with a subject may have a deterrent effect on important research. Although it is true that a human being may be the source of a marketable cell line, it is the researcher who has identified and fostered the discovery. Researchers may well question the utility of conducting such studies, particularly if research subjects demand a significant share of the financial gain.

A possible change in the DHHS informed consent regulations could be made to modify the prohibition on the use of exculpatory language to permit research subjects to waive any rights to commercial gain stemming from research findings. This provision should be clearly worded, and the waiver of such rights must be free of undue influence and coercion. Research subjects should

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understand exactly what rights are being waived. They should also understand that should they decide not to waive their rights to commercial gain, they will not be denied treatment to which they are otherwise entitled. In appropriate cases, research subjects should be informed that their decision not to waive their rights to commercial gain may disqualify them as participants. When such situations arise, subjects should be told why a nonwaiver is a basis for exclusion from a study and what compensation is available to the subject who agrees to a waiver. This may take the form of an offer of a lump sum of funds to compensate the subject for waiving rights to marketable, human research material.

Permitting the use of enforceable, exculpatory language regarding commercial gain could actually enhance the rights and welfare of subjects. It is possible that researchers and sponsors may be far more protective of the source of their human tissues and cells if they need not share financial gain with subjects.

Giving subjects the opportunity to waive their right to financial gain from marketing products derived from their biological material does not obviate the need for informed consent. Indeed, with certain safeguards in place, there should be no hesitancy in permitting exculpatory language through which an "informed" subject waives legal right to possible legal rights to financial gain.

Latent Discovery of Commercial Gain

If the prospect of financial gain does not become apparent until subjects have become deeply involved in the project, generally accepted principles of human research hold that the researcher has a duty to disclose this information as soon as possible. It represents a logical perpetuation of the consent process, particularly when a latent discovery may have a dramatic impact on the original terms of consent.

Support for this view can be found in the current regulation (45 CFR 46.116(5)) that authorizes an IRB to require additional disclosures regarding "significant new findings" that may affect a subject's willingness to continue in research. An additional disclosure with respect to the effect of withdrawal from a study could be made based on 45 CFR 46.116(4).

Role of the Institutional Review Board

If additional disclosure requirements and the use of exculpatory clauses are added to the consent process, IRBs will have a greater role. Current regulations indicate that when potential subjects are vulnerable to undue influence or coercion, the IRB should make certain that there are safeguards to protect their rights and welfare (45 CFR 46.111(b)). This role becomes particularly important when potential commercial gain is involved. It is equally important when researchers intend to use exculpatory language and seek waivers from subjects to commercial gain.

What could be included in these added safeguards? The following are examples of additional protections that could enhance the rights and welfare of subjects:

- careful review by the IRB of information to be disseminated to subjects to make certain that it details in comprehensive terms what constitutes "commercial gain";
- monitoring the consent process on a random basis to make certain that subjects are receiving approved information and that there is no evidence of undue influence or coercion;
- in the case of subjects who may be vulnerable to undue influence or coercion, the IRB could require the appointment of an advocate whose duties would be similar to those for children who are wards under 45 CFR 46.409(b); and
- followup procedures, such as random outcome screening to compare the experience of subjects at the conclusion of the study with research protocols, information sheets, and consent documentation presented to participants at the outset of the project.

Should researchers determine in the course of a study that a significant likelihood exists for potential gain, the regulations could require them to report this fact to the IRB. Investigators could then present to the IRB the information they intend to disclose to subjects. This could be approved by the IRB along with written information sheets and consent documents.

Documentation Requirements

Disclosure of potential commercial gain and the use of exculpatory language reinforce the need to accurately document consent. This does not have to be a so-called "long form" consent; a "short form" consent document would suffice (45 CFR 46.117(b)).

The major difficulty with current documentation is that the IRB has the ability to waive the requirement for signed consent. This can occur when the only record linking the research with the subject is the consent form and the principal risk involved is a potential breach of confidentiality. Similarly, documentation can be waived when a study involves no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context (45 CFR 46.117(c)).

With the prospect of commercial gain and the use of exculpatory language, some type of documentation could be required to safeguard the rights of all concerned. First, IRBs could be prohibited from waiving consent form documentation when studies involve the prospect of commercial gain or the use of exculpatory language. This solution, however, does not alleviate the concern for a potential breach of confidentiality found in the current regulations. The problem is compounded when an additional consent authorization is required for cases in which commercial gain is discovered subsequent to the first consent. Requiring consent forms in this case could represent a serious concern for subject confidentiality. A breach of confidentiality in this situation could make the subjects a target for unscrupulous persons who for their own financial gain might identify the participants carrying marketable biological substances. A possible solution to this problem is to require researchers to use extra safeguards to maintain confidentiality of research subject information, but this idea may not be realistic.

Another option is to leave the current regulation unchanged, but add a proviso that a waiver approved by an IRB constitutes a rebuttable presumption of valid consent. This would be important if allegations ever arose claiming that the subject was not informed about commercial gain or that the subject did not waive his right to commercial gain. Unless the subject could rebut the inference of proper disclosure of information or a properly obtained waiver, the presumption of valid consent would stand. If such a recommendation is deemed practical, further review would be necessary to make certain that it does not offend Federal evidentiary provisions.

A third option would be to require a detailed note in the subject's record. This would eliminate the need for consent forms when minimal risk is involved. It also minimizes concern about breach of confidentiality when consent forms are the sole link between the subject and the study. With the use of a carefully designed system of identification codes, a detailed note in the record offers less chance of identifying a subject than does a traditional consent form. A detailed note in the subject's record is also a practical means of documenting disclosures and waivers regarding commercial gain made subsequent to the entry of participants into the study. When confronted with a detailed note in his or her record, the subject will be hard-pressed to prove lack of disclosure or a waiver to commercial gain. A detailed note in a subject's record would have certain advantages over a standardized consent form. For instance, a note could contain information tailored to the specific subject, a feature often impractical in standard forms.

SUMMARY AND CONCLUSIONS

Consent must generally be obtained from patients and research subjects prior to specimen removal for treatment or experimentation. Informed consent represents a two-way flow of information between the physician or researcher and the patient or research subject in order to communicate the facts necessary for the patient to decide on a method of treatment and for the research subject to decide whether to participate in the research.

The common law has developed two different theories of consent: the traditional view, based on the law of battery; and a more modern theory based on the law of negligence. Several States have enacted consent laws, many of which are concerned with setting requirements for information disclosure. Federal regulations provide protection of human subjects in federally sponsored research. The Federal policy requires each research institution to establish and operate Institutional Review Boards that have oversight authority over research using human subjects and sets certain requirements that investigators must follow to obtain informed consent prior to and during research.

Questions arise as to whether disclosing the prospect of potential commercial gain should be required as part of the informed consent process. Arguments favoring such disclosure include the concept that research subjects should have the right to decide what to do with their own tissues and cells, and that current regulations require disclosure of significant new findings developed during the course of research which may relate to the subject's willingness to continue participation. Arguments against disclosure regarding potential commercial gain include the possibility that any commercial gain is highly speculative, that disclosure would hamper a research subject from reaching an informed decision free of the undue influence that monetary gain might provide, and the possibility that subjects might endanger their health and skew research results by hiding facts from researchers so they can participate in research that may provide financial remuneration.

Current Federal regulations contain two provisions that concern the marketing of tissues and cells. The first excludes certain types of specimens (e.g., existing data, documents, records, pathological exams, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects) from the regulatory requirements. The other provision prohibits the use of exculpatory language through which the subject is made to waive or appear to waive any of the subject's legal rights. Either or both of these provisions could be revised to achieve certain results, or additional disclosure requirements could be included in the regulations to be used when the prospect of commercial gain is relevant. If additional disclosure requirements and the use of exculpatory clauses are added to the consent process, Institutional Review Boards will have a greater responsibility in oversight of research.

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Chapter 7

Economic Considerations

"Every time we obtain a sample . . . we make sure there is a piece of paper . . . I take all the risks and put $25 million of investment into the research. I don't want the patient then saying, 'Yeah, but it came from me.' "

—Michael S. Ostrach
Vice President, Cetus Corp.
The Baltimore Sun, Apr. 6, 1986

"In nearly every case, the cells will never yield anything of commercial value. But lotteries do have winners. In exceptional circumstances, one person's cells will have a special property that makes them uniquely valuable."

—Edward Dolnick
The New Republic 195(3739):16, 1986

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Chapter 7

Economic Considerations

The fundamental economic question that arises when considering the use of human tissues and cells in biotechnological research and commerce is that of payments to sources. And if sources are to be paid, what factors will enter into the price calculation? This chapter summarizes economic arguments for and against payments for provision of human tissues and cells, analyzes the organization of provision of human biological materials along market and nonmarket lines, and describes the potential role of nonprofit institutions in brokering human biological materials.

PAYMENTS TO SOURCES

On economic grounds, it is possible to argue both for and against paying the sources of human biological materials. Arguments over payments for human biological materials used in biotechnological research and commerce echo the debate that has gone on for many years over donations of kidneys for transplantation and donations of blood for transfusion and therapeutic products. Five principal issues are essential in the debate:

- the equity of production and distribution,
- the added costs of payments to sources and costs associated with that process,
- social goals (the merits of an altruistic system of donations versus a market system),
- safety and quality (both of the source and the biological materials), and
- potential shortages or inefficiencies resulting from a nonmarket system or from changing from a nonmarket system to a market system.

Of these issues, two appear to be central. Issues of equity argue in favor of a system of payments to sources. On the other hand, the added costs of payments to sources and associated costs argue against such a payment system. The factors related to social goals, safety and quality, and shortages do not now offer compelling support either for or against paying sources.

Equity

The equity of a system can be considered from both the production and distribution sides. On the production side, one issue is whether any of the participants are receiving an inequitable return for their services or products. On the distribution side, issues arise regarding access to the services or products by parties who seek them.

Production of Human Biological Materials

It can be argued that some sources are not entitled to the value of the tissues and cells they provide because they do nothing to develop the materials into a valuable product. Diseased tissue, for example, is actually a threat and sources are willing to pay a physician to excise it. By this reasoning, sources perceive such human biological materials as less than worthless, and it is only the intervention of the researcher that gives the tissue value. It is the researcher, therefore, who should legitimately realize the economic value of the tissue.

On the other hand, it could be argued that the sources of tissues and cells are entitled to the value of any resources ultimately derived from them. This view holds that human beings have the right to treat certain physical parts of their own bodies, particularly regenerative parts, as objects for possession, gift, and trade (1). As the commercial potential of biotechnology emerges, this viewpoint could become increasingly relevant. If it is possible to determine or estimate the potential value of biological materials, then as information is distributed, patients, or their agents, will come to know the values of tissues and cells they may possess and they will expect adequate recompense.

Distribution of Human Biological Materials

Researchers desiring human tissues and cells from other researchers, especially at other institutions, must rely on the willingness of other researchers and institutions to cooperate. By custom and ideology, the main incentive to this cooperation is the scientific commitment to the free flow of ideas and materials. To date, the system has operated fairly efficiently. However, as biotechnological products and processes are being commercialized this free flow of information and materials occasionally is being curtailed and in many cases is becoming more formal. There may also be shortages of human tissues and cells for basic research if the incentives to cooperate prove insufficient to motivate researchers to go to the trouble of supplying fellow researchers.

When access to a good is not based on market values, other nonmarket forms of distribution can arise. One unfortunate feature of many nonmarket systems is corruption, sometimes expressed in side payments. The kidney procurement system provides an example. In principle, access to kidneys is determined on the basis of criteria such as length of time on the waiting list, tissue type, need, and age. At least one medical center, however, placed wealthy patients needing kidneys ahead of other patients, with equal needs, on its waiting list (9).

Added Costs

Two types of additional costs would be incurred if sources were compensated for their specimens: the actual compensation to the sources and the cost of administering the program (also called "transaction costs"). These costs could add significant burdens to the process of developing biotechnological products and processes from human tissues and cells.

Payments to sources could range from large sums that might be awarded to a handful of sources who have rare tissues to small sums given to the many sources of more common tissues. In either case, because tissues and cells generally are obtained as byproducts of needed medical treatment, most sources are unlikely to refuse access to their tissues and cells on grounds of insufficient payment. Thus, payments will likely easily exceed the amount required to draw forth the services of an adequate number of sources. For this reason, the actual compensation to sources is unlikely to have a large economic impact on the biotechnological uses of human biological materials.

The transaction costs associated with paying sources, however, are likely to dwarf the costs of actual payments to the sources. Studies employing human cell lines, for example, may take years to complete and the final commercial application may be the result of accumulated research based, in part, on a number of different cell lines. The transaction costs incurred by a researcher to maintain records of the origin of all the cell lines leading to the development of a particular cell line with commercial applications could be sizable (6). Furthermore, transaction costs will be incurred for the many uses of cell lines and cells that do not have direct commercial applications (see ch. 2) or even have no value. For instance, it is possible that cells from a specific patient will not successfully become established in culture for technical reasons. Or cells might become contaminated with bacteria. Thus, some tissue samples—probably the overwhelming majority—will never be developed into cell lines and yet would incur significant transaction costs (6).

In addition, because many preliminary experiments must be carried out before a commercial application is discovered or developed, it would be difficult to negotiate a value for a particular human tissue at the time it is obtained. Scientists also would have considerable difficulty establishing the relative value of individual cell lines that lead to commercial application. Some experiments with cell lines will contribute more to commercial application than others, and it would be difficult to assess their value a priori or even after the fact (6).

Many of the cell lines used in research are used for purposes other than developing commercial products. Cell lines are used to test whether particular substances are required for cells to grow or to test the response of cells to exogenous agents. The physiology or the morphology of the cell might be explored, or the cells might be used as a means to propagate viruses. Cells are also used as model systems for screening carcinogens or teratogens. In addition, cell lines can be used in research from which negative findings contribute to knowledge, but do not result in a commercial product. Finally, many cell lines are used as untreated controls in research as the cell line in question is manipulated. Even if any of these applications resulted in commercialization, it is likely that many cell lines from many patients would have been used in the research. The transaction costs borne by the researcher in tracking the patient origin of the cells used for research collateral to actual commercialization and negotiating their value would be high (6).

Another potential problem associated with a payment system is the harm it could have on information exchange among scientists. As the informal distribution system operates today, cell lines are shared among researchers to confirm research results or to begin new research projects. Negotiations over the transfer and value of property rights for cell lines could reduce the exchange of information among scientists (6).

Another area of transaction costs might also occur—the cost of negotiating between the researcher or physician and patient over transferring property rights. These negotiations would create sizable costs for all parties even if the debated cell line never has a commercial application. For instance, because the patient and the researcher or commercial firm have different degrees of knowledge regarding commercial applications of cell lines, the patient may have to retain knowledgeable third parties or consultants. The principle is the same as hiring a knowledgeable broker to aid the purchase and sale of stocks and bonds (6). An additional factor is that conflicts over the distribution and value of rights may impose additional stress on sick patients.

Social Goals

Social goals also enter into the debate over the merits of a market system versus a nonmarket, or altruistic, system. Arguments in favor of payments for human tissues and cells are based on three lines of reasoning. First, the primary issue can be viewed as a need to save lives; in the case of organs, this need is not met by free donations because too few donations are made so payment is necessary (2). Second, requiring altruism where substances of great value are concerned leads to black market activity and, in fact, the opposite of the desired behavior. Third, altruism alone may not be sufficient motivation to provide enough materials to meet demand. Altruism is not necessarily the primary factor in the decision to donate, for example, when pressure is placed on a sibling or parent to provide a kidney to a relative in need (3,5).

Inherent in most arguments against paying sources for bodily materials is the widespread moral repugnance at the notion of a market in human body parts. This repugnance is most strongly felt in the case of organ sales, where, for example, permanent physical damage to the organ vendor may result. An additional argument relates to the relationship between patient and physician (or researcher). Introducing monetary motives on either part could affect the bond of trust between patient and doctor. On the other hand, the altruistic provision of human biological materials by one person to another in order to save a life may contribute to the bonds that hold communities together (11).

Safety and Quality

The issues of safety and quality probably are not major concerns for most biotechnological uses of human biological materials. Most such tissues and cells are removed in the course of needed surgery for the patient's benefit, so the motives of the source (or payment to him) is not likely to affect either the source's safety or the quality of the biological materials obtained.

In those few instances where provision of human tissues and cells may be discretionary, payment could influence the safety of both the source and the recipient of human biological materials. When the procurement activity itself poses risks to the source, the potential for harm would likely be exacerbated by the promise of payment. Motivated by the promise of payment, for example, individuals might accept a measure of medical risk to provide their kidneys for transplantation, in effect becoming organ mines for wealthier people in need of kidneys. Similarly, when commercial whole blood collectors were in business in the United States there were numerous reported cases of excessive bleeding of donors and lower quality blood.

The quality of human specimens can affect the safety of the recipient. There has been a dramatic increase in scientists' awareness of the potential for viral contamination of human-derived biologicals in recent years. Blood products have transmitted hepatitis and acquired immune deficiency syndrome, and pituitary hormone preparations have transmitted Creutzfeld-Jakob disease to previously healthy recipients. Similar problems can be expected to arise with any tissues and cells of human origin. Viewed from one perspective, commercial pressures could aggravate quality problems, while altruistic systems could help ensure good quality (11). On the other hand, quality may be problematic precisely because there is insufficient commercialization and because of the protection from liability that voluntarism might afford to those people responsible for procuring and dispensing human tissues and cells (8).

Shortages

At present, there is no apparent shortage in the availability of human tissues and cells for biotechnological use. Shortages that may develop in the current nonmarket system are likely to be a function of inherent shortages of a particular type of tissue in the population, or a problem of access and transportation. As the techniques of biotechnology and the biotechnology industry mature, however, this situation may change. In a time of shortages, two mechanisms to draw forth an adequate supply of human tissues and cells for research purposes are: 1) the motivation of sources by altruism (e.g., the possibility that the research will lead to a cure for a serious illness); and 2) payment to sources.

Opponents of payments to sources argue that a market system could exacerbate shortages of needed human samples. They fear that any hint of monetary concerns would discourage donations by eliminating the altruistic motivation and potential sources would hold out for the highest bidder.

Proponents of paying sources, in contrast, argue that if altruism is not the primary motive in providing human tissues and cells, payments to sources might draw forth a larger supply. One example of this was seen in the early years of the whole blood market, when insufficient supply by altruistic donors was supplemented by supplies from paid donors. Nonprofit blood collectors have succeeded in the last 20 years in nurturing the motive of altruism in donors, so now blood shortages, while still occurring seasonally, no longer are a major problem.

Those in favor of payments to sources argue the case for a market system most strongly in the context of cadaver organ donations. Patients are indeed dying because of the shortages of certain cadaver organs, such as livers and hearts. Proponents of payments for cadaver organs argue that such payments would be virtually certain to increase the number of cadaver organ donations. Although there might be some decrease in organ donations from people whose primary motivation was humanitarian, there would likely be a net gain in the number of organs available (2,3).

A market system can be the most efficient method of handling shortages because a free market tends to equate demand and supply at some equilibrium price level. Systems in which prices are regulated at below market values generally suffer shortages, often relying on the altruism of providers or direct coercion to obtain the socially desired result. Nevertheless, where an economic activity is already organized along nonmarket lines and the primary motivation of participants is altruism, and where the demand for the item is fixed, any introduction of market activities may not elicit an increased supply of donations—it may even have the undesired effect of reducing the level of donations. The precise effect that introducing a market system would have on supply of human biologicals remains a matter of speculation.

MARKET v. NONMARKET SYSTEMS

The present system for developing human-derived commercial biotechnology products contains both market and nonmarket activities, although there are few instances of actual payment among researchers for human tissues and cells. Some researchers and physicians, however, do have consulting relationships with biotechnology or pharmaceutical companies which provide access to tissues and cells derived from humans or products of research involving human materials.

At university research centers, scientists are generally required to share the fruits of their research with the university. Where university researchers and biotechnology companies have a defined research relationship, the potential value of the human biological materials may be shared. In many cases, however, biotechnology firms do not themselves purchase undeveloped human tissue. Instead, they may negotiate with a researcher who has already developed a cell line, gene probe, or something else of potential value. The structure of these deals can either be direct purchase, royalty agreements, or any of a number of other possibilities.

By the time a biotechnology company enters the picture and begins to negotiate with a researcher, there is generally already reason to believe that the product is of potential value. Since the researcher is an informed negotiator, he is likely to recognize the potential value of the undeveloped tissue. In this situation, the researcher—rather than the biotechnology company or human source—may reap the value of the undeveloped tissue. Should a market arise where undeveloped tissue could be bought and sold, any added value that is currently being realized by the researcher, physician, university, or biotechnology company might be recaptured by the source of the human tissues and cells.

At present, there is no widespread movement toward a change in the existing system of free provision of human tissues and cells for use in research and commerce in biotechnology. Stimulus for such a change may come from: 1) judicial decisions resulting from current litigation and any additional cases that might arise in the future, and 2) a greater interest in the uses of human tissues and cells in biotechnology as the commercial profitability of the industry begins to be realized (10).

There are several ways to organize a market system in human biological materials to minimize the problems that might arise. For instance, payments to sources could be made prospectively, before commercialization is a likely outcome of the research. At that time, neither physician/researcher nor patient/subject will have reason to believe that the cells are especially valuable. People who believe that individual specimen sources should share more fully in commercial successes may object to this approach, however, particularly if they are patients (to whom a fiduciary duty is owed). They might prefer to make a large payment to the one fortunate source whose tissues or cells are ultimately incorporated into an invention, but give no payment to the majority whose specimens were used and discarded. In a way, this is a form of lottery, raising the possibility that participants would be unduly influenced by the lure of a prize. Payment to one fortunate source also fails to recognize the contributions of those sources whose specimens were also essential components of the research leading to the final invention, even though not a part of the invention itself.

If a prospective payment approach were used, payments could be made on the basis of a flat fee to patients and research participants for sale of their specimens. (While many research subjects are now paid for their participation, they are not explicitly paid for their tissue. Patients generally are not paid for their specimens, either.) This prospective payment approach would result in uniform payments to all specimen sources who do not waive payment and would require only minimal paperwork and recordkeeping. The amount of research money needed to make these payments could be calculated from the projected number of patient/subject specimens stated in the research proposal.

Alternatively, payments that vary among sources could be negotiated by the physician/researcher and each patient/subject early in a research project. If negotiated before either party knows whether the specimen has valuable characteristics or whether a commercial product will result, the fee is likely to be low. In cases involving common types of cells, no negotiation at all would be necessary: the researcher would budget a fixed amount per specimen and would refuse to pay more since there are numerous sources of appropriate tissue. However, the researcher would also have the flexibility to pay a higher fee to individuals whose tissues and cells have unusual characteristics. This approach lets market forces affect the transactions between researchers and sources and gives researchers significant discretion in determining an appropriate payment, but it may result in increased time resolving negotiations and perhaps even bidding among competing researchers.

When tissues or cells are purchased from a source at the time of surgical excision, rather than later when a commercial product has been developed, neither the patient nor the researcher knows whether the tissue has value and the tissue's value is its expected value. This expected value depends on the probability that a commercially viable product can be developed. In principle, then, this value could be estimated at the time of excision and the amount, probably nominal, could be paid to the source. The cost would be similar to the costs pharmaceutical companies have incurred in conducting worldwide searches for chemical samples. An alternative form of agreement could provide an initial, nominal amount to the source with the promise of a percentage of any future profits if commercial gain is realized.

If the patient objects to the payment offered and if the researcher does not value the tissue more highly, then no deal would be struck. Since there is no reason to believe a priori that the tissue is unusual, neither researcher nor subject would have concern that something of value was being lost. If the patient has some reason to think his tissue is rare, or if he is a risk taker and unwilling to accept the researcher's statistically fair offer, he would have every right to go to the expense of having the tissue examined himself.

Prospective payment to sources conceivably could be used by researchers engaged in applied research where the objective is to develop a commercially viable product. Much research, however, is not directed toward developing a product. How would researchers engaged in such basic research obtain their tissue? It would clearly be desirable for these researchers to be given tissue by patients at no cost and undoubtedly some sources will be motivated by altruism. The problem for these sources will be whether to trust the researcher when he tells them that the goals of the research are noncommercial. Further complicating the matter is the fact that the researcher may not be able to anticipate where the research will lead and may end up with an unanticipated commercial product after all.

Other approaches could be used to encourage the researcher to reveal his true intentions regarding his research objectives. For instance, a researcher might have two informed consent forms. If he thinks there is commercial potential, then he buys the right from the patient with a commercial consent form. If he thinks that his research has no commercial potential, then he and the patient sign a free-donation consent form. However, the noncommercial consent agreement would contain clauses with penalties for the researcher should his research lead to a commercial product. The beneficiary of the penalty might be the nonprofit university where the research is performed. This structure could provide incentive to encourage the researcher to reveal his best guess as to where the research is likely to lead.

A market system might also operate on the basis of retrospective payment to sources—that is, payment after prospects for commercialization are recognized or realized. Inherent in a system of retrospective payment is the possibility that a source could have unrealistic expectations about the likelihood of commercial success, the degree of profitability, or the relative importance (and value) of the raw material as compared to other aspects of the research and development effort. Retrospective payments could encourage sources to engage in a form of extortion, demanding unreasonable prices for consent to use their specimens, confident that companies have already invested years of research and development (and millions of dollars) in the product. A retrospective negotiation process would require the assistance of attorneys representing both parties.

Neither prospective nor retrospective payment appears to be prohibited by the physician's fiduciary duty to his patient. What is more likely to be an unacceptable breach of that duty would be a failure to disclose information about commercial potential or provide for some fair system of compensation.

Any design of a feasible system of payments to sources would require further information and analysis. A useful and relevant model to consider where unpaid and paid donations exist side-by-side is the blood and plasma donation system currently operating in the United States. For most of their activities, the whole blood and plasma sectors operate in rather different spheres. However, the largely nonprofit whole blood sector (which relies on unpaid donations) and the largely commercial plasma sector (which pays its sources) do compete in the sale of finished plasma products. This example of a hybrid nonprofit/commercial organization of economic activity may prove instructive in considering payments to sources of human tissues and cells for biotechnology uses.

THE ROLE OF NONPROFIT ORGANIZATIONS

Nonprofit organizations may play an important role in the marketing of human tissues and cells, just as they have in the procurement and distribution of blood and organs. A clear and unequivocal nonprofit organization for procuring and distributing human biological materials may be necessary to preserve the trust between sources and recipients and ensure the continued provision of human specimens for research. Providing tissue to an assuredly nonprofit organization may allay the suspicions of sources who want to support basic research but who do not want any one person to benefit financially from their contribution.

Nonprofit institutions often step in to fill the need when markets fail to deliver a sufficient quantity of certain goods that are clearly in demand. In many instances, it is a public nonprofit institution—the government—that provides the service. The government also can intervene less directly to regulate markets by controlling prices, requiring that providers be licensed, or declaring certain goods to be nonmarketable.

Private nonprofit enterprises[1] are the form of organization most relevant to the provision and receipt of human tissues and cells. There are two general ways to finance nonprofit organizations. Some nonprofits, such as CARE or the American Red Cross, receive their income primarily in the form of grants or donations. These organizations are called donative nonprofits. In contrast, commercial nonprofits, such as many hospitals and daycare centers, receive their income primarily from the sale of services. In the case of donative nonprofits, the patrons are the donors. The patrons of commercial nonprofits are the customers receiving the services (7).

What characteristics of an activity make it more suitable to nonprofit than for-profit organization? Why, for example, do people wishing to provide food assistance to impoverished persons overseas donate money to an organization such as CARE when they could engage the services of an experienced commercial grocery distributor? The main reason appears to be that with certain products consumers are unable to evaluate accurately whether the promised good or service has been delivered. In such circumstances the market may provide insufficient discipline for a profit-seeking producer. The key element seems to be trust. In the preceding example, the source does not know and is not in contact with the party receiving the food. Consequently, the source would have great difficulty verifying that the grocery distributor had fulfilled its part of the agreement. The source therefore needs a trusted organization to fulfill the agreement. Because of the legal constraints under which it must operate, a nonprofit is likely to serve in that role better than its for-profit counterpart. Nonprofit enterprises therefore can be seen as a response to a particular kind of market failure.

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[1] It is important to note that if profits are defined as the excess of revenues over costs, then private nonprofit enterprises also earn profits. The difference between profit and nonprofit institutions lies in whether the earnings are distributed to those who have control over them.

Commercial nonprofits, such as hospitals, differ from donative nonprofits in that the bulk of their income is in the form of payments made by patrons in direct exchange for services. Since the recipient of the service is also the source, the type of market failure described in the food aid example (resulting from the distance between the source and the recipient) does not occur. The consumer, however, may still prefer to deal with a commercial nonprofit firm rather than a for-profit firm because the services sought are of such a nature, or provided under such circumstances, that the consumer must necessarily entrust a great deal of discretion to the producer—a discretion that the consumer may be in a poor position to police.

It can be expected that when the profit motive is eliminated, a price is paid in terms of incentives. Nonprofit firms are often slower in meeting increased demand and less efficient in their use of inputs than for-profit firms. Furthermore, despite the limitations placed on them, some nonprofits probably do distribute some of their net earnings through inflated salaries and perquisites. Nonetheless, where the consumer is in a poor position to judge the services he is receiving, any for-profit organization of production and distribution is likely to rate second best to a nonprofit enterprise despite the expected efficiency losses.

Alternatives to Nonprofit Institutions

Many goods and services are not easily evaluated by consumers and yet are commonly provided by for-profit firms. Medicinal drugs are one example, as are the services of doctors, lawyers, automobile mechanics, and television repairmen. But these services are generally small and discrete and consumers can switch suppliers relatively easily if they become dissatisfied. Furthermore, special institutions have arisen to provide additional protection for consumers. Doctors and lawyers, for example, must be licensed and are subject to some supervision and discipline from their respective professional organizations. Drugs prescribed by doctors are subject to Federal regulation for safety and efficacy. Nonprofit distributors are likely to arise where such protective mechanisms have not developed or are inadequate.

Regulation of for-profit organizations can help maintain the strengths of for-profit organizations while limiting their flaws. This regulation can either be imposed by the government or can be imposed contractually through free negotiation directly between the parties. Limits on rates of return, for example, are often imposed on natural monopolies such as public utilities. Under such regulation, prices are restricted to a level that permits the firm's shareholders to earn a specified rate of return on their investment while protecting the public good. Firms subject to regulation of their rates of return can be viewed as special cases of nonprofit organizations.

Nonprofit Institutions and the Government

Nonprofit organizations have four principal inherent weaknesses:

- Nonprofit institutions may be severely limited in their ability to raise capital since they are unable to sell equity shares. They must rely instead on donations, retained earnings, and debt for capital financing.
- While commercial nonprofit entities must legally use the entire sum paid by the consumer to produce services, the consumer has no assurance that the services he pays for will be provided to him. Patients in private hospital rooms, for example, often subsidize ward patients through their high room and board charges.
- Profits are an important motivator of management efficiency, and nonprofit institutions might be expected to be somewhat less vigilant in eliminating unnecessary expenses than their for-profit counterparts.
- The profit motive is a powerful incentive for ensuring that firms enter an industry and expand when the demand for the industry's product increases. Stripped of this motive, nonprofit organizations might be more sluggish in responding to changed demand.

In response to these problems, a number of services commonly provided by nonprofit organizations are frequently also undertaken by government, such as education and hospital care. The taxing power of the government gives it a strong advantage over nonprofits. Government organizations also have access to capital and a degree of accountability not necessarily found in all types of nonprofits.

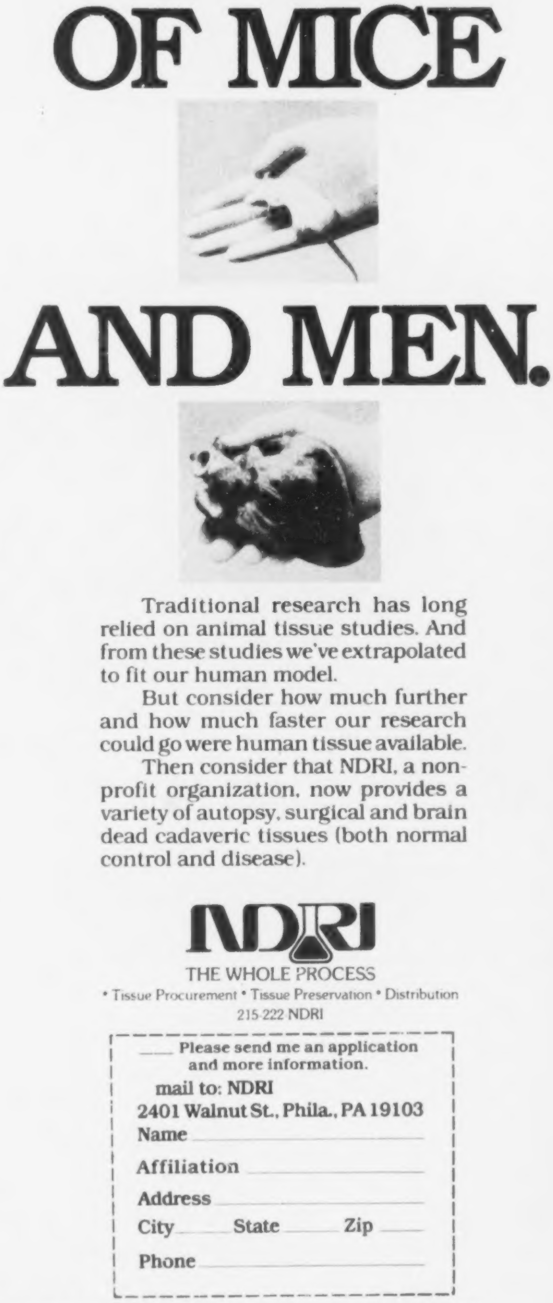
At least one nonprofit corporation that procures and distributes human biological materials is supported by the Federal Government. The National Disease Research Interchange (NDRI; Philadelphia, PA) is a nonprofit corporation founded in 1980 to advance the procurement, preservation, and distribution of tissues and organs for research (figure 7-1). It was established by the National Institutes of Health and the Pew Memorial Trust in response to requests from the biomedical community for regular access to human tissues in order to corroborate animal studies. Since 1981, NDRI has distributed more than 20,000 tissue samples to research laboratories in the United States. Researchers are asked to reimburse NDRI for tissues. Typical charges range from $10 for eye tissue (e.g., iris) and $200 for pancreatic tissue to variable amounts for intestinal tissue (4).

Interaction of For-Profit and Nonprofit Institutions

Different types of human tissues and cells are now used for a variety of nonprofit and profit purposes. Human samples are used by the pharmaceutical industry to produce drugs, by transplant surgeons to transplant vital and nonvital organs, and by hospitals to transfuse blood. In each instance, the human material can be considered a factor in a production process.

Four key features of these markets, however, distinguish human biological materials from many other goods and services. First, there is no necessary connection between the value of the human biological material and the price of the material. By law, certain types of human materials, such as organs for transplantation, are not permitted

Figure 14.—Promotional Material, National Disease Research Interchange



OF MICE

AND MEN.

Traditional research has long relied on animal tissue studies. And from these studies we've extrapolated to fit our human model.

But consider how much further and how much faster our research could go were human tissue available.

Then consider that NDRI, a nonprofit organization, now provides a variety of autopsy, surgical and brain dead cadaveric tissues (both normal control and disease).

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mail to: NDRI
2401 Walnut St., Phila., PA 19103

Name ______

Affiliation ______

Address ______

City ______ State ______ Zip ______

Phone ______

SOURCE: National Disease Research Interchange, Philadelphia, PA.

to be sold; by fiat, therefore, the price of these resources is zero. Diseased human tissues and cells used in research have also, by custom, been free to investigators. For healthy tissue that researchers recruit from sources, compensation varies, but usually covers only time and inconvenience. Second, there may be nonprice regulation of who may provide human biological materials, how the transaction is to occur (e.g., through informed consent), and who receives the final product. Third, even when the price of human specimens is zero, there are a significant number of persons with altruistic motives who willingly offer their tissue. Fourth, many of the organizations involved in producing the final product are nonprofit organizations.

This distribution scheme is a direct consequence of the extraordinarily high symbolic value placed on human tissues and cells that often requires suppliers of these materials to be motivated by altruism alone. However, while altruism is required to be the motivator of supply for many types of human biological materials, no such requirement is made of other participants in the production process, which may at times include for-profit actors. To control this production process, some regulation of prices, rates of return, and distribution may be imposed. The regulation can take several forms and involve public and private nonprofit organizations.

As described in chapter 5, the law is unclear in defining the rights relating to human biological materials. In the case of organs for transplant, the law only specifies that the source does not have the right to sell it. The law does not specify who may in fact reap the economic value of the organ. Legislating that the source does not have the right to sell an organ and that it can only be transferred at a price of zero does not, however, reduce the value of the organ to zero. What it does, instead, is transfer the value of the organ from the source to other parties.[2] These could be the owners of the other factors of production, the entity that produces the final product, the purchasers or recipients of the final product, or all of these parties. How the parties share in the value of the zero-priced factor depends on the supply and demand conditions prevailing in the market and on the degree of control the producer has over the market.

SUMMARY AND CONCLUSIONS

The traditional relationships between sources and researchers, and among researchers at different institutions, have been informal and involved free exchange or transfers. Today, however, the techniques of biotechnology and the potential for profits and scientific recognition have introduced issues of commercialization into various uses of human tissues and cells.

At present, there is no widespread sentiment favoring a move toward a market system for human tissues and cells. Two principal factors will likely determine whether a change occurs in the current system of free donation of human tissues and cells for use in biotechnological research and commerce. A change could arise from: 1) judicial decisions in present or future cases under litigation, or 2) a greater public interest in the uses of human biological materials in biotechnology as the commercial profitability of the biotechnology industry begins to be realized.

From the point of view of equity, a market structure has a strong appeal because it eliminates the potential windfall realized by parties receiving the free donation. On the other hand, the magnitude of the transaction costs associated with payment to sources may be sufficient to deter any forays into a market structure. Perhaps the most likely development is that there will be little practical difference between a market and nonmarket structure for handling human tissues and cells: because of the great uncertainty about the value of any one sample of human tissues or cells and the small percentage of useful tissues and cells, the market price for untested tissue will be nominal.

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[2] Suppose, for example, that a market for transplantable kidneys existed. There are three parties to the transaction—the donor, the surgical/hospital team, and the recipient—and they are able to accomplish the transaction at prices agreeable to all. The amount required by the family of the kidney donor to proffer the kidney is $50,000, the amount required by the surgical/hospital team to bring forth its services is $100,000, and the kidney recipient is willing to pay $150,000. Suppose further that a law is passed requiring all transactions in kidneys to be gifts, thereby prohibiting the kidney donor's family from selling the kidney and reaping its economic value of $50,000. Who will now realize this value? The intent of the legislation was that the value of the kidney be transferred as a gift from the kidney donor to the recipient, with the transplant ultimately costing the recipient only $100,000. Yet, because nothing is done to ensure this outcome, a different outcome is possible. Depending on the conditions of the transplantable kidney market, it may be possible for the surgical/hospital team to realize the value entirely by charging the recipient $150,000. Of course, this transfer of the value of the kidney from the donor to the surgical/hospital team would be subject to a broad ethical debate.

For the present nonmarket system to continue to operate successfully, a clear and unequivocal nonprofit organization of procurement and distribution of human tissues and cells may be necessary to preserve the trust between sources and takers and to ensure the continued supply of donations of human biological materials for research purposes.

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Chapter 8

Ethical Considerations

"It is time to start acknowledging that people's body parts are their personal property."

—Lori B. Andrews
Hastings Center Report 16:5, 1986

"We may be more than mere protoplasm, but we're nothing without our bodies (at least in this world). Putting a price on the priceless, even a high price, actually cheapens it. So we don't approve of selling our body parts; and the body isn't quite property."

—Thomas H. Murray
Discover, March, 1986

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Chapter 8

Ethical Considerations

INTRODUCTION

The use of human tissues and cells in biological research raises important ethical issues about how these materials are obtained, transformed, and possibly commercialized. **Although these issues are new, there are significant moral and ethical traditions from which to develop guidelines about the ways in which human biological materials *ought* to be developed or exchanged.** The absence of established customs or patterns for the development and exchange of these materials is due, at least in part, to the relatively new potential for profits to be derived from the development of human cells and tissue into cell lines or gene probes. This potential creates novel questions about the best courses of action that should be taken by physicians, patients, and others concerning the transfer of human biological materials. The following hypothetical case study indicates some of the ways in which new questions about the proper transfer and use of human tissues and cells can affect the relationship between doctor and patient.

Hypothetical Case Study

Ms. Doe is a 42-year-old female who visits her gynecologist once a year for a routine pelvic exam, Pap smear, and mammography. In recent years, her physician's premiums for malpractice insurance have soared. Ms. Doe suspects that this is one of the reasons why she must now sign a sheaf of consent forms and waivers concerning the possible hazards of exposure to radiation, the possible use of her tissues and cells, and so on. She has come to regard the relationship between doctor and patient as one in which she is asked to be both vulnerable and unprotected. She waives her right to every sort of recourse save one prior to her visit with the doctor. She is determined not to be completely outsmarted and has purposely not waived her rights to any commercial interests that may result from the use of her cells or developed cell lines.

Dr. Ray is a 50-year-old obstetrician/gynecologist beset with the problems and conflicts associated with conducting what had once been a satisfying practice in the modern technological world. She has been sued three times in the course of her 25 years of practice and in each case the charges have been dropped. Nonetheless, these experiences have caused her considerable stress and some humiliation in her relationships with her colleagues. She no longer derives the satisfaction that she once did in her relationships with patients because she can no longer practice in a trusting fashion. When she first began her practice, she believed that her obligations were to be of benefit to patients and, above all, to do no harm. In recent years, she has had to change her approach from telling her patients what she thinks they need to know to providing them with an abundance of information in order to allow for their autonomous choices as recipients of health care.

Advances in biotechnology offer both Ms. Doe and Dr. Ray some potential recompense for what they both view as modern encroachments on what had heretofore been a relatively unencumbered and trusting relationship. Both have heard that it is possible and occasionally profitable to patent cell products developed from unique cervical cells and wonder if the yearly routine Pap smear could be an opportunity for financial gain.

It is not farfetched to consider the ways in which modern developments in biotechnology might transform the relationship between doctor and patient. It is now possible to obtain something of value in any medical procedure that involves collecting a patient's tissues or cells. This possibility seems to entail new obligations regarding informed consent. The nature of these obligations, however, is a subject of some debate.

List of Ethical Questions

This chapter addresses the following questions:

- Is it ethical for human tissues and cells to be developed into commercial products?
- If it is ethical for human tissues and cells to be developed into commercial products, what are the necessary ethical conditions for such transactions?
- What is the relationship between the identity of a person and his tissues and cells?
- Are there any limits or restrictions on the use of human tissues and cells?
- Does an individual retain rights or interests in his tissues and cells after they are cast off as waste, surgically extracted, or otherwise relinquished?

The underlying question is whether or not the buying and selling of undeveloped human cells or developed cell lines and gene probes could result in substantial benefits or harms for individual human beings. It may be that anxieties about whether it is ethical for bodily materials to be bought and sold or about how justice should be preserved in the distribution of profits are largely an American phenomenon. In Japan, for example, a loan shark gives his clients the "opportunity" to repay him in kidneys. In the Philippines, prisoners attempt to obtain earlier paroles by "donating" kidneys. In Bombay, India, a mother sold her kidney for $7,000 to buy a dowry for her daughters, a clock, a TV set, and a swivel fan (22).

In this country, the combination of for-profit and nonprofit markets encompasses the sometimes competing values of private enterprise and public good (see ch. 7). If private enterprise and the public good were always synonymous, then the question of whether it is proper or fair for researchers to profit from human biological materials would not arise. This chapter discusses not only whether any harms might result if human tissues and cells are bought and sold, but also how profits that accrue from any commercialization might be fairly or justly distributed.

THE ETHICS OF BUYING AND SELLING BODIES AND THEIR PARTS

Are human biological materials objects for commerce, things that may properly be bought and sold? There are three broad ethical grounds for objecting to or supporting commercial activities in human biological materials. These parallel, but only roughly, the generally accepted ethical principles of **respect for persons, beneficence**, and **justice.**

First is respect for persons: the idea that trade in human materials ought to be limited to the extent that the body is part of the basic dignity of human beings. If the body is indivisible from that which makes up personhood, the same respect is due the body that is due persons. Conversely, if the body is considered incidental to the essence of moral personhood, trade in the body is not protected by the ethical principle of respect for persons.

The second moral principle is beneficence. Would commercialization of human materials (perhaps of specific kinds) be more beneficial than a ban on such commercialization? Proposals for markets in human tissues, for example, could be justified on the grounds that they would lead to a preponderance of good results over bad. On the other hand, objections to the same markets could likewise be couched in consequentialist (outcome-oriented), beneficence-based terms.

The third principle is justice. A societal commitment to fairness and equality may be relevant to determining the moral acceptability of commerce in human body parts. It may be that much of the public repugnance to a market in human tissues stems from a sense that the limit on permissible inequalities would be breached by such a market.

The Principle of Respect for Persons

The principle of respect for persons can be illustrated by the work of four moral theorists: two have theological roots, two have secular backgrounds. In addition, two emphasize the moral importance of the body, and two view human biology as incidental to the moral nature of human beings. The theologians are Paul Ramsey and Joseph Fletcher; the philosophers are Leon Kass and H. Tristram Engelhardt, Jr.

When these individuals have addressed commercialization, it usually has been in the context of organs for transplantation. Each, however, has important views about the body and its relationship to moral personhood that illuminate the ethical debate about the use of human tissues and cells in biotechnology (14).

Paul Ramsey

Paul Ramsey, a Christian theologian, argues that man is a "sacredness" in his bodily life. For Ramsey, respect for the human body as an inseparable part of the person is an important moral duty grounded in the respect due to all persons created by God (18). Ramsey has reservations about the morality of organ donations by living donors. He requires that due weight be given to the physical harm done to the donor since the only human life we know to respect, protect, and serve in medical care is physical life. In particular, giving an organ is an act of charity and never an obligation.

Ramsey has equally deep qualms about policies that would remove organs from the newly dead without the consent of the donor while living and the family upon death. Even with consent, he cautions that human beings should not begin to think of their bodies as a group of parts to be given, taken away, or, worst of all, sold. Ramsey believes that **human beings exist in their bodies and that respect for the body is indivisible from respect for the person.** Ramsey has a basic concern about humankind's tendency to regard the body as an instrument or as incidental to the moral person. He states:

> There are many refined and subtle ways by which men [and women] may be encouraged or allowed to treat themselves as parts only, or collections of parts, in the service of medical progress or societal value to come. In terms of our vision of man and his relation to community, there may be little to choose between the blood and soil, organic view of the Nazis and the technological, "spare parts," mechanistic analogies of the present day (18).

Ramsey criticizes those Protestant and Catholic theologians who, he believes, give too little emphasis to the fact of human embodiment. They contribute, he says, to the technological view of human bodily existence. Their writings simply affirm the dualism of person and body that influences contemporary views.

In addition, Ramsey is opposed to commercialization of the human body, or at least of its vital organs. His principle reason stems from his view of the body's irrevocable connection to the person; he sees the body as a sacredness in the biological order. This requires that it be treated with respect. This view also makes the commercialization of the body morally repugnant.

Ramsey incorporates into his ethics the notion of a "quasi-property right"—the right of kin to control the disposition of the body for burial in Anglo-American common law. (See ch. 5 for a discussion of legal aspects of this right.) He argues that this right is "quasi" in that possession for commercial purposes is still denied to any claimant (the man himself or his kin). It is a sort of "property" in that possession for a certain human and familial purpose is legally protected. This purpose is the positive human value and interest at stake—a protection of the poor or the upwardly mobile from commercial exploitation even with the consent of the person whose body it is, or was. Ramsey states that there is no opposition too strong against the potential abuses of a market in human flesh.

Ramsey is so committed to the idea of sacredness and bodily integrity that he offers, only half-facetiously, the proposal that organs donated by living donors be regarded as merely on loan, to be returned to the giver when the recipient dies. Ramsey makes this proposal to emphasize the importance of bodily integrity and the wrong done when integrity is violated—even for such a great good as preserving the life of another. For him, no great preponderance of good could justify harming a live donor against his charitable will. His discussion of living organ donors asks: Does the body belong to the person? His answer: Yes.

For living or cadaver donors, may parts of the body be sold? His answer: No (14).

Joseph Fletcher

In contrast to Paul Ramsey's view of the ethical centrality of the human body, theologian Joseph Fletcher gives biology some emphasis, but does not assign much, if any, moral significance to it. To Fletcher, **the body appears to be merely a necessary condition for the pursuit of the truly important things about being human. Its significance is only instrumental, not essential.**

A recurrent theme in Fletcher's work is a preference for human control over natural processes, for design and choice over chance, for reason over those things indifferent to reason. Fletcher asserts that being truly human involves knowing one's circumstances (e.g., one's physical nature) and controlling circumstances toward rationally chosen ends (5).

Fletcher's equation of artifice and control with moral stature suggests that he advocates the least natural course as the most morally elevated one, that the artificiality of certain means of conception make them, for that reason, preferable to natural means. He states:

> To be a person, to have moral being, is to have the capacity for intelligent causal action. It means to be free of physiology! It is precisely persons—and not souls or bodies or glands or human biology—that count with God and come first in ethics (5).

The relative unimportance of the body to moral personhood is reinforced in Fletcher's seminal article about "indicators of personhood"(7). He names 15 positive and 5 negative criteria. Fourteen of the fifteen positive criteria are descriptions of various capacities—e.g., self-awareness, curiosity, concern for others. Only one directly addresses the body—a functioning neocortex. It is clear that this physiological requirement is important only because the neocortex is the physiological substratum—the enabling condition—of the other 14 criteria.

Of the five negative criteria—those things that he asserts are not central to moral personhood—three may be taken to pertain to the human body: persons are not non- or anti-artificial; they are not essentially sexual; and they are not essentially parental (7). In Fletcher's view, it is reasonable and possible to be thoroughly human and favor technology, to have the human species survive without sexuality, and to be fully personal without reproducing.

Fletcher's desire to move the body outside of the moral compass is even more accentuated in subsequent writings reflecting further on indicators for humanhood. He says that neocortical function is the key to humanness, the essential trait necessary to all other traits (7).

Given Fletcher's views about the moral insignificance of the body and his celebration of control and artifice, it is unlikely he would object to the commercialization of the body or its parts based on respect for persons. He might have other objections, but they would have to be on quite different grounds. His view of the body and its relation to the moral person could not support any strong objection to using it for commercial gain.

Leon Kass

Leon Kass, a physician and philosopher, objects to those whom he calls corporealists, that is, those for whom there is nothing but the body. He also objects to theorists of personhood, consciousness, and autonomy who treat the essential human being as pure will and reason, as if bodily life counted for nothing (10). Kass states that the former confines man too much to mindless nature; the latter treats man in isolation, even from his own nature (10).

In his book, *Toward a More Natural Science*, Kass develops a philosophy of medicine and medical ethics based on what he believes are insights that come from a right understanding of the body. It is completely secular, and in that respect it is distinct from both Ramsey and Fletcher. But in its rejection of a mind/body dualism and its embrace of a concept of the body that stresses its dignity, Kass has much in common with Ramsey and little with Fletcher. He finds part of his inspiration in the way physicians regard the body:

> Doctors respect the integrity of the body not only because and if the patient wants or allows them to. They respect and minister to bodily wholeness because they recognize, at least tacitly, what a wonderful and awe-inspiring—not to say sacred—thing the healthy living human body is (10).

On secular rather than theological grounds, Kass stands with Ramsey in tying human embodiment to human moral worthiness. He states that human dignity rests on acknowledging the necessity of human embodiment. What is the relationship of the human being to his body: that of the owner to property? He does not explicitly answer this question but he makes clear his skepticism about treating the body as commercial property. Discussing reproductive technologies in general and surrogate motherhood for pay specifically, Kass states that the buying and selling of human flesh and the dehumanized uses of the human body ought not to be encouraged (10). This position is tied to his general repugnance at the notion of owning living nature per se. He doubts the wisdom of permitting the patenting of life and worries about individuals owning entire living kinds, e.g., micro-organisms. He sees no natural stopping place between bacterium and homo sapiens, once the ownership of living nature is permitted. He asks:

> If a genetically engineered organism may be owned *because* it was genetically engineered, what would we conclude about a genetically altered or engineered human being? (10).

Kass refuses to separate the body out from what gives human beings their dignity and offers the premise that one can learn a great deal about human dignity and moral conduct from looking carefully at what the body means. He is reluctant to permit commercialization of the body or to treat living nature in general as something that should be reduced to mere property. Taken together, **these views create an argument that links the body to human dignity so strongly as to raise doubts about the moral acceptability of commercializing the human body.**

H. Tristram Engelhardt, Jr.

H. Tristram Engelhardt, Jr., a physician and philosopher, holds a secular view of the body that has much more in common with the theologian, Fletcher, than with the philosopher, Kass. Human beings have no interest, he says, in preserving mere biological life as an end in itself. In contrast to the brain, and particularly the neocortex, the body is a complex, integrated mechanism that sustains the life of the brain, which serves as a basis for the life of a person (4). But all of the body's parts, aside from the higher parts of the brain, can be replaced. The particular features of the body are in this sense more incidental than essential. Engelhardt has no difficulty counting the computer HAL in the movie *2001* as a person. His views on personhood and brain transplants are consistent with this (i.e., personhood goes with consciousness, with the brain and not the body) as well as his view on the proper definition of death. He agrees with Fletcher that in humans the person does not survive the destruction of the neocortex. From all of this, it is clear that for Engelhardt the body is morally important only insofar as it embodies the life of the person. Engelhardt stresses that it is in and through our bodies that we are in the world, have our relations with others, and realize our concrete purposes in life (3). Still, persons can objectify their bodies, measure them according to personal goals, replace them, and even sell them.

Because persons are at the core of morality and because persons are in the world through their bodies and have their bodies as their cardinal possessions, individuals cannot do whatever they please to the bodies of others. Engelhardt states that one cannot respect other moral agents, while being willing to destroy their embodiment or their unique place in the world (4). Respect for persons, then, provides a minimal protection against unwanted physical violence to the bodies of human beings.

Engelhardt's arguments regarding the limits of State authority lead to his explicit views on the commercialization of the body. In contrast to thinkers like Ramsey and Kass for whom the special dignity of the body places it outside the realm of those things that may be bought and sold, Engelhardt cites the philosophers Hegel and Locke to develop his claim that the human body is the quintessential example of property. He then argues that we have a right to trade our bodies commercially. In fact, he argues that, if anything, our right to trade other material objects is inferior to and less clear than our right to trade our bodies. He also would permit indentured servitude, as it exists, for example, when one receives support for education in exchange for a commitment to military service.

For Engelhardt, these rights are based on consent. He states that persons own themselves and own other persons insofar as they have agreed to be owned (4). He explicitly denies the authority of governments to forbid commercial trade in bodies and their parts. He states that the authority of governments is suspect, insofar as they "(r)estrict the choice of free individuals without their consent" (e.g., attempts to forbid the sale of human organs) (4). Should the State try to prevent such transactions, he defends a fundamental moral right to participate in the black market (4). According to Engelhardt, individuals own their bodies and may commercialize them as they wish. There is no State authority for interfering in that commercialization, and there is a moral right, all else being equal, to defy any such efforts at State control. Engelhardt contends that it cannot be presumed that individuals have consented to such governmental control of their bodies by virtue of their participation in the State.

Although religious views may be thought to be the key dividing line between those who consider the body an essential and irremovable part of personhood and those who give it much less moral weight, this brief analysis of the views of four theorists shows that this is not the case. Rather, **it appears that the idea that the brain and the neocortex are the morally important stuff of personhood is held by those who do not oppose commercialization of the body.**

The Principle of Beneficence

The relevance of the principle of beneficence to the debate can be understood by considering this fundamental question: **would commercialization of human materials be more beneficial than a ban on such commercialization?** Even allowing for imperfections, one could argue that a market in human tissues and cells would be the most efficient system of determining production and allocation. A market would permit the quantity produced to match the quantity demanded at an equilibrium price that reflects the value of the material to sellers and buyers. However, it is important to consider whether there are any beneficence-based reasons to object to a market in human tissues and cells (14).

Beneficence-Based Objections to Commercialization

There are two general types of objections to commercialization based on the principle of beneficence. The first focuses on basic assumptions about the importance of freedom and rationality; the second grants these assumptions, but argues that wider, indirect effects are preponderantly negative (14).

Arguments of the first type deny that individuals maximize their own well-being through market transactions. There are four objections of this type:

1. Critics of commercialization argue that the assumption that people are rational consumers is dubious. There is ample evidence of irrational human behavior in markets and elsewhere. While this may not seem important when the commodity being traded is a videocassette recorder or cake mix, irrational trade in human tissues, cells, and cell products is a more serious matter.
2. While the assumption that people are free and rational might be reasonable for most adults, there will be large classes of people, including children, the mentally ill, and the mentally disabled, for whom this assumption is clearly unjustified. These people might participate in either production or allocation markets. Given their inability to consent to the use of their body, including invasive procedures necessary to obtain commercially valuable materials, their participation as sellers seems particularly morally questionable. Decisions would need to be made about whether to ban such people as suppliers, make provisions for their limited participation, or endure the spectacle of unlimited use of such nonconsenting suppliers.
3. In every human interaction, including all market interactions, there is the possibility of

abuse—of fraud, misrepresentation, coercion, and the like. This is not peculiar to markets in human materials, but it may be that abuse in this realm is more morally repugnant than it would be with other goods.

4. There may be a discrepancy between what people desire and what they need; that is, between what even fully rational and free consumers might pursue in a market, and what those individuals need to promote their genuine well-being. Therefore, it is possible that a market might be consistent with human desires but inconsistent with the human good.

The second type of beneficence-based objections go on to ask about the wider effects of commercialization, particularly of the human body:

1. Commercialization of the body will lead to disrespect and devaluation of the human body in general. This argument will not be especially persuasive to those who believe that the biological body does not deserve such respect in the first place (e.g., Fletcher) or who argue that such regulations fall outside of the moral authority of the State (e.g., Engelhardt).
2. Commercialization will somehow threaten important ideals of equality, not through any explicit declaration in favor of inequality, but because in a society where wealth is unequally distributed, the costs of production and benefits of allocation are likely to be unequally distributed as well. Whether such inequities come to be seen as morally unacceptable will depend on a number of complex factors having to do with the prevailing ideals of the culture, the history of related decisions, and the nature of the good being allocated. When the poor, for example, are the suppliers of human biological materials and the wealthy are the beneficiaries (e.g., if production and allocation of transplantable kidneys were accomplished through markets), the resulting correlation between risks and poverty, benefits and wealth, would challenge a very important conception of equality in this country.
3. Moving from the concept of gift to a market in human tissues and cells carries with it such important losses to the common good that they will, on the whole, outweigh the immediate benefits (12,18).
4. In the specific case of human biological materials donated for research to nonprofit institutions (e.g., university-based biomedical research), the shift from a gift to a market basis could have damaging consequences in the cost and availability of such materials, public perception of and generosity toward biomedical researchers, and increased suspicion of health providers.

Principles of Justice

Distinct questions of justice as fair and equal treatment arise when considering the acquisition, development, and allocation of human tissues and cells. To complicate matters further, there are several ideals or theories of justice, each of which commands a certain amount of respect and adherents. **Since our society appears to subscribe to several, sometimes incompatible ideals of justice, there will be no easy way to list the ethical implications of commercializing human biologicals from a "correct" theory of justice.** It is possible, however, to contrast two important, opposed views: the libertarian view and the egalitarian view (14).

The Libertarian View

Libertarian theorists emphasize the processes of exchange as based on free consent, they minimize the importance of whatever distribution results from a series of fair exchanges, and they hold that the State does not have the authority to interfere in most market transactions (4,15). On the other hand, more egalitarian theorists believe that there are constraints on permissible exchanges, and they also believe that there may be specific limitations on the institutions a just society may have (19) or on the distribution of at least some goods—especially those goods necessary to the fulfillment of basic human needs (2,24).

The libertarian view of justice and the commercialization of the body is intimately tied to the importance of the concepts of respect for persons and private property. This view places a fundamental emphasis on autonomy, understood as the free choice of rational persons based on rights to privacy and noninterference by the government where parties involved freely consent. The idea of property has as its paradigm case one's ownership of one's own body (4). Given these premises, interfering with commercial trade in one's own biological materials would be perhaps the clearest and gravest affront to justice imaginable.

Given the libertarian view, selling oneself freely to another does not involve a violation of the principle of autonomy, so such transactions should fall within the protected privacy of free individuals. In addition, if one sells oneself at the right price and under the proper circumstances, one would expect to maximize the balance of benefits over harms. However, the point in principle is that free individuals should be able to dispose of themselves freely (4).

According to this view, if this results in the poor selling and the rich buying, so be it; interfering with the free choices of individuals is a violation of justice. The pattern of distribution is not relevant to justice; indeed, the very notion of "distributive" justice, of unjust patterns of distribution obtained from exchanges not in themselves unjust, seems incoherent in this theory.

The libertarian view of justice follows directly from the concept of the person as individual, autonomous, and free, and from the notion that respecting persons means most of all not interfering in whatever transactions to which rational individuals agree. **The libertarian theory of justice says in effect that commercial trade in body parts is the essence of justice, and that those who would interfere with it have an exceedingly heavy burden of proof on their shoulders.** The more traditional maxims of distributive justice—to each according to need, worth, merit, or work—are replaced by "to each according to the agreements he has freely made" (4).

The Egalitarian View

The egalitatian theory of justice contrasts with the libertarian view. Egalitarian theory is based on a powerful and clear view of respect for persons. This theory emphasizes concepts of natural or human rights. These human rights are prima facie claims, to be respected even though not explicitly invoked.

These human rights are based on a concept of individual moral worth as inalienable and as absolute. According to this view, all humans are of equal and immeasurable moral worth. Egalitarians argue for the proposition that one person's well-being is as valuable as any other's and one person's freedom is as valuable as any other's. From this follows the claim of the prima facie equality of a person's right to well-being and freedom (24).

One egalitarian offers this definition of justice: "An action is just if, and only if, it is prescribed exclusively with regard to the rights of all whom it affects" (24). Egalitarians argue that some inequalities can be justified precisely on the grounds of justice; that is, that the very reasons for saying that human beings have equal moral worth and equal rights to well-being and freedom can also, under certain empirical circumstances, justify limited forms of inequality.

By showing that certain inequalities may be justified within an egalitarian theory of justice, it is possible to identify and condemn unjustified inequalities. This is accomplished by examining practices to see if they deny or diminish the equal moral worth of individuals or groups of persons, or if they otherwise enhance or impede satisfying the demands of justice.

To the extent that commercial trade in human tissues and cells makes people feel that they are inferior to others, this practice would be unjust. Pricing the body and its parts, which would probably lead to the poor selling more than the rich, could also have this effect.

The arguments come full circle. **If one believes that the body is merely incidental to what is morally significant about persons—their rationality, capacity to choose, and freedom—then those aspects of commercialization likely to lead to differential participation in the body-market will not seem offensive, precisely because the body is not particularly connected to a person's moral worth. If, on the other hand, one believes that respect for persons includes respect for the human body, then those empirical properties of the market do pose a threat to justice (14).**

THE MORAL STATUS OF BODIES AND THEIR PARTS

Philosophical and religious traditions offer a number of alternatives for thinking about the body and its parts in relationship to the human person. These traditions provide a basis on which to gather insights about the uses and transfer of human tissues and cells.

Philosophical Perspectives

The nature of the relationship between human identity, personhood, and the mind to the body is a problem that has classical roots in Western philosophy. Although the early Greek Atomists held that the human mind was made of actual material, the idea that the mind is nonspatial has dominated philosophical thinking since the time of Plato. The view that the human mind and body exist as a duality was developed in some detail by Rene Descartes in the 17th century. Cartesian dualism holds that the essence of a person is an immaterial, nonspatial substance or mind that can, in theory, exist apart from the body. During the lifetime of an individual, mind and body are one but this is incidental and not necessary to the existence of mind.

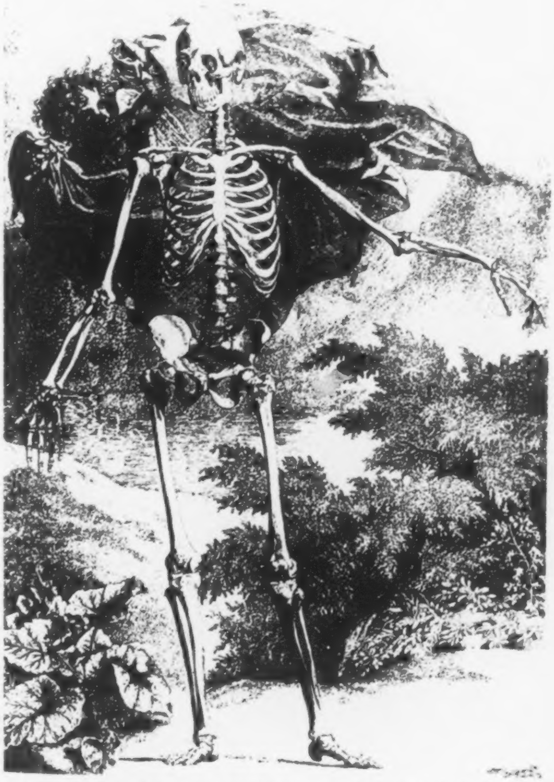
From a Cartesian point of view, human tissues and cells are valuable only to the extent that they provide a temporary substrate or basis for the existence of the human person. The relationship between the human person and a particular tissue or cell is not essential, particularly if these materials are replenishable. This is not to say that Cartesians would be reluctant to attach a monetary value to such materials. In fact, they may be quite inclined to make tissues and cells the object of commerce because there is no great significance attached to such materials in terms of the human mind, personality, or identity.

There are at least two primary alternatives to Cartesian dualism. One alternative view is that the human mind and some specific biological material (e.g., the human brain) are intimately connected so that it is impossible for the mind to exist apart from the presence of brain tissues and cells such as neurons. In this case, one might value certain kinds of human tissues and cells above others. The donation of brain tissue might be viewed as more central to the essence of a person than the donation of skin tissue.

A second alternative to Cartesian dualism is that mind or the essence of the human person is intimately connected to all of the biological material that comprises the human body. In this case, the essence of the person or identity is tied up in each and every cell and tissue, so no one type of human tissue would be considered more valuable than any other. In fact, the genetic identity of an individual person can be discerned from any one somatic cell.

It is not clear that either of these alternatives to Cartesian dualism necessarily precludes the use

Figure 15.—The Human Skeleton v. the Human Person



SOURCE: *Albinus on Anatomy*, by Beverly Hale and Terence Coyle.

of human tissues and cells in commerce. The materialist may in one case attach a higher price to certain kinds of cells or he might hold that each and every tissue is so valuable that all human biological material should be expensive. In addition, **whether one is a Cartesian or not, it may be possible to object to the buying and selling of human tissues and cells based on social justice or other considerations that are separate from the question of how the essence of a human person is related to the body.**

Selected Religious Perspectives

There are three reasons to examine religious perspectives when developing public policies in a pluralistic society. One reason is historical: many existing laws regarding bodies and their parts have been influenced by religious sources. To understand these laws, it is important to identify the beliefs and values that support them. Second, religious traditions shape the ethical values of many people. These traditions influence whether some uses of bodily parts or materials are viewed as ethically acceptable or unacceptable. A third, closely related reason is that religion and religious organizations are an important facet of our society and they have to be considered when policymakers try to determine which policies are politically feasible. Extreme opposition from religious organizations sometimes may render a policy infeasible from a political standpoint (1).

Because of variations among and within Judaism, Catholicism, and Protestantism, it is difficult to speak of a "Judeo-Christian tradition" unless that is taken to mean a common source (the Hebrew Bible/Old Testament) and some common, though very general, themes (1). These themes are based on the relationship between God and human beings.

The Old Testament states that God created the world, including human beings, as good. Human beings themselves were created "in the image of God" (Genesis 1:26f; cf.5:1 and 9:6). This is the basis of the theological doctrine of "imago dei"or the image of God. Although imago dei has been variously interpreted as reason, free will, or spiritual capacities, some theologians have objected to the concentration on intellectual and spiritual aspects of humanity to the neglect of the external body. Some have even argued that the image of God is the body, while others have argued that it is a combination of the spiritual and the physical in a psychophysical unity. Jewish and Christian thought and practice as a whole views the person as an animated body. At times, however, Judaism and Christianity have also appropriated Hellenistic convictions about the separation of soul and body; sometimes their beliefs and practices represent a combination of themes (25).

Among the numerous ethical implications of different interpretations of the image of God, some are especially important for this study. The Genesis passage connects creation in the image of God with God's authorization of human "dominion" over the rest of creation. Humans are in, but are distinguished from, the rest of nature. If, as in the royal ideology of the ancient Near East, humans are God's representatives in parts of his kingdom, their rule should be like God's and should never be exploitative. Their dominion is not to be viewed as domination but as stewardship or trusteeship. **As stewards and trustees, human beings do not have unlimited power. God has set limits on what human beings may do with and to their own bodies and those of others** (1). Genesis 9:6, for example, connects the prohibition of taking human life with creation in God's image.

Arguments against suicide in Judaism and Christianity often draw on analogies between relationships between God and human life, on the one hand, and ordinary relationships, on the other. Many of these analogies involve property relationships (e.g., life is a gift or loan from God) or personal or role relationships (e.g., human beings are God's children, servants, or sentinels). While Jewish and Christian traditions rule out suicide and some uses of the body such as prostitution, they do not clearly prohibit slavery, even though its convictions, particularly about the creation of all human beings in God's image, could be invoked in opposition to slavery (1).

Finally, respect for the cadaver is significantly connected to the human beings' creation in God's image: Jews and Christians respect the body of the dead as symbolic of the human person and his dignity (8). This respect recognizes and supports (within limits) the aversion to tampering with the body, whether living or dead.

The language of the image of God has often focused on what is distinctive about human beings, particularly their use of reason, exercise of will, and making decisions. Respect for persons is one way to state the implications of the theological doctrine of the imago dei, but it entails respect for embodied human beings, not simply their wills, and it is not unlimited self-determination or autonomy because it is severely limited by God's creation and will. In practice, it is often very difficult to determine what actions are required by the principle of respect for persons, as an expression of the imago dei (1). This point is evident in the following analysis of specific Jewish, Catholic, and Protestant beliefs and practices regarding the body, its parts, and materials.

Judaism

In Judaism, as well as in Catholicism and Protestantism, there is little, if any, direct discussion of the issues arising from the modern use of human tissues and cells. Hence it is necessary to ferret out concepts and principles in the myriad rules that Jewish tradition has developed regarding the living human body and the cadaver. Several relevant concepts and principles can be discerned in the laws of burial. Also relevant is the interpretation of the rules of the "halakah" (the body of Jewish law supplementing Scripture) through analogical arguments about cases.

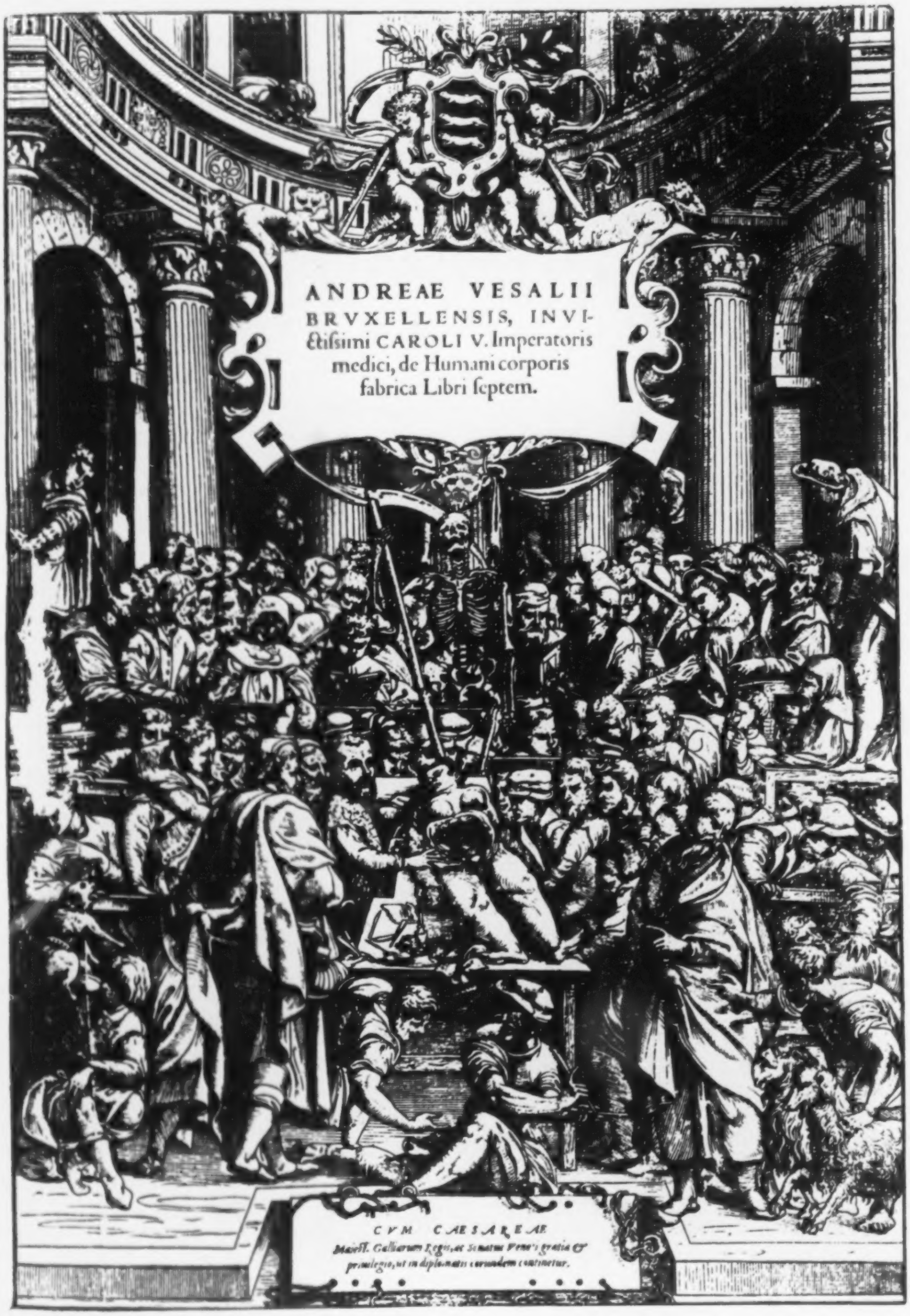
According to Jewish law, there are three major prohibitions regarding the cadaver: it is impermissible to mutilate the cadaver (and thus, according to many, to cremate it), to use or derive any benefit from the cadaver, and to delay the interment of the cadaver or any of its parts (17,20). These prohibitions against desecration derive from God's creation of human beings in his own image (21). How are these prohibitions interpreted and applied? In particular, are they absolute? Any prohibition in Jewish law, except for murder, sexual immorality, and idolatry, may be overridden in order to save human life. Saving human life is a paramount imperative—"Thou shalt not stand idly by the blood of thy neighbor" (Leviticus 19:16)—and it justifies some actions that would appear to be prohibited regarding the cadaver.

Under Jewish law, autopsies are generally opposed even when performed to establish the cause of death or to increase medical knowledge in general. An autopsy is permitted, however, to answer a specific question that would contribute to the immediate improved care of patients (21). When a patient dies, for example, while suffering from cancer and receiving an experimental treatment, it may be important to determine whether the drug was in part responsible for the death. The emphasis falls on the immediacy of the benefit to be gained. Within the Jewish tradition, the cadaver merits the same dignity, respect, and consideration that would be accorded a living patient undergoing an operation (21). Organs should not be removed from the body, except where absolutely necessary for the information sought, and any removed organs must be returned to the body for burial except for small sections necessary for pathology examinations. Any part of a dead body must be buried because any person who comes into contact with it is ritually defiled.

The priority of saving human life allows for considerable flexibility in the application of Jewish law to technological developments such as organ transplantation. The tradition emphasizes that the source of the organs must be dead according to criteria of absence of respiration and absence of cardiovascular pulsation—obviously these criteria pose problems for organ transplantation—and it stresses the decedent's act of donation (though familial donations are not precluded). Some commentators view the prohibitions against the use of a dead body as not applying to a removed organ which "lives" again when it is successfully transplanted into a recipient (20).

Within the Jewish tradition there would appear to be opposition to tissue banks on the grounds that a recipient is not immediately available, but cornea banks have been viewed as acceptable on the grounds that it is highly probable that the cornea will be used immediately because so many potential recipients are at hand. It would not be easy, however, to extend this argument to cover research on human tissues, cells, and developed

Figure 16.—Dissection of the Human Corpse


ANDREAE VESALII
BRVXELLENSIS, INVIctiſsimi CAROLI V. Imperatoris
medici, de Humani corporis
fabrica Libri ſeptem.
CVM CAESAREAE
Maieſt. Galliarum Regis, ac Senatus Veneti gratia &
privilegio, ut in diplomatis eorundem continetur.

SOURCE: *De Humani Corporis Fabrica*, 1555.

cell lines and gene probes because it is difficult to predict benefits, which, in any event, would only accrue to patients in the future.

It is permissible for living persons to donate a kidney to save someone's life or to donate blood to a blood bank. Even though there are prohibitions against intentionally wounding oneself or forfeiting one's life to save another, most interpretations of Jewish law hold that one is allowed or even obligated to place oneself into a possibly dangerous situation to save his fellow man from certain death (21). This is a risk-benefit analysis, in which the probability of saving the recipient's life is substantially greater than the risk to the donor's life or health. Blood donation is viewed similarly, even though the donor may have no specific recipient in mind and the blood may be stored for a time. Here again the needs of potential recipients are so great that there is a reasonable certainty that the blood will be used to save life, while the risks to the donor are minimal.

In general, the requirements for exemption from the prohibitions regarding the cadaver or the living person focus on the probability of immediate rescue of human life. Both the prohibitions and the exceptions are based on the dignity of human beings as created in the image of God. Extensions of the exceptions to banking corneas or blood suggest that some indirect and delayed possibilities may be available. However, as indicated in the preceding discussion, it would be difficult—though not impossible—to extend them so far as to include research and commercialization on human tissues and cells or cell lines and gene probes. Such an extension would depend on the probability of significantly benefiting human beings through research.

Roman Catholicism

In general, the Catholic Church holds that notable or major excised parts of the body should be buried. Transplantation of organs and tissues from cadavers generally has been accepted. Donation of organs and tissues has been viewed as praiseworthy, though not obligatory, and the benefit of donation need not be as direct or as immediate as Jewish law suggests.

From a Catholic perspective, since human beings are merely the administrators of their lives, bodily members, and functions, their power to dispose of these things is limited (11). In this context, the principle of totality limits what people may do to their bodies and parts. The principle of totality indicates that a diseased part of the body can be removed for the benefit of the totality or whole body (13). This doctrine was subsequently applied to the amputation of a healthy human limb. A modern formulation of this doctrine appears in Pope Pius XI's *Casti Connubii* (1930):

> Furthermore, Christian doctrine establishes, and the light of human reason makes it most clear, that private individuals have no other power over the members of their bodies than that which pertains to their natural ends; and they are not free to destroy or mutilate their members, or in any other way render themselves unfit for their natural functions, except when no other provision can be made for the good of the whole body.

Because this formulation of the principle of totality appears to warrant mutilation only for the physical benefit of the person's body as a whole, it also appears to rule out removal of an organ to benefit another person. However, many theologians have come to believe that mutilation is ethically appropriate when it is for the good of the whole person, not simply of the body.

Some critics contend that appeals to psychological or spiritual benefits to the donor to justify organ donation undermines the appropriate moral-religious constraints on the human use of bodies and their parts (18). One Jesuit moral theologian rejects both of these charges: Richard McCormick contends, first, that a donor's benefit (psychological or spiritual wholeness) is not necessarily identical with the donor's motivation (charity), and second, that these psychological and spiritual attributes of the donor only establish the moral context of organ donation, not the justifiability of particular transplants. The justifiability of particular transplants depends on the proportionality of benefits and burdens to the recipient and to the donor (13).

In a statement that invoked an analogy with the sale of blood, Pope Pius XII refused to rule out all compensation for organs and tissues:

> Moreover, must one, as is often done, refuse on principle all compensation? This question remains unanswered. It cannot be doubted that grave abuses could occur if payment is demanded. But it would be going too far to declare immoral every acceptance or every demand of payment. The case is similar to blood transfusions. It is commendable for the donor to refuse recompense: it is not necessarily a fault to accept it (16).

Catholicism, like Judaism and Protestantism, emphasizes the dignity that belongs to human beings and to their physical remains after death. This dignity is derived from their creation in the image of God. Representing the image of God, human beings are stewards or administrators of their lives but their actions are limited by God's law. Some of these limits have been expanded in recent years in response to technological developments. In general, charitable acts of donation are praised, whether they are directed toward specific individuals or tissue banks (e.g., a blood bank), but they are subject to evaluation from the standpoint of proportional or relative good (e.g., kidney donation).

Protestantism

Although there are variations within both Judaism and Roman Catholicism, they are not as extensive as in Protestantism, which encompasses so many different religious groups. After examining some Jewish, Catholic, and Protestant positions in the late 1960s, Joseph Fletcher lamented, "as we often find in these matters of specific or concrete moral questions, there is no Protestant discussion on surgery, autopsy, and other mutilative procedures—not even on the ethics of transplant donation (6)." Modern Protestants tend to emphasize the principle of respect for persons even more than Catholicism, with its emphasis on the ends of nature, and Judaism, with its strong emphasis on the tradition of interpretation of the law. However, Protestants generally have recognized limits to what people may do to their bodies even when they have disagreed about what those limits are. The philosopher Immanuel Kant offered one extreme formulation:

> It is a form of partial self-murder to deprive oneself of an integral part, for example, to give away or sell a tooth to be transplanted into another person's mouth or to be castrated in order to make a more comfortable living as a singer and so forth. But to have a dead or diseased organ amputated when it endangers one's life or to have something cut off which is a part, but not an organ, of the body (e.g., one's hair) cannot be considered a wrong against one's own person—although a woman who cuts her hair in order to sell it is not altogether free from guilt (9).

Protestants generally do not believe that there are any special limits on what may be done to cadavers. Protestants, like Jews and Catholics, recognize limits expressed in the language of respect and dignity. One Protestant commentator argues that rituals are needed even after a cadaver's organs have been donated as "a testimony to the privileged place of the body in acts of love (12)." For the most part, Protestants tend to conceive most of the major ethical problems in this area in relation to consent, which they see as a requirement of the principle of respect for persons.

In the treatment of living persons, Protestants tend to emphasize the virtues of love or charitable consent. Many theologians would grant greater latitude to competent people making decisions about their own organs to benefit others than to surrogate decisionmakers donating organs (e.g., kidneys) from persons such as children or institutionalized, mentally retarded, or insane people. However, several Protestants have argued that charitable consent still allows too much latitude in permissible donations. At least one Protestant theologian appeals to a strand of Biblical tradition, also strongly affirmed by Judaism, that emphasizes the integrity of the flesh and opposes Cartesian mentalism and dualism, which he fears could lead, for example, to donation of a heart by a living person (18). Although the independent value of bodily integrity clearly rules out a heart donation from a living person, its other limits are not very clear. As in Judaism and Catholicism, one of the main requirements for organ donation would be proportionality as expressed in a risk-benefit analysis.

In sketching out the implications of these traditions, it is important to recall the distinction between ethically acceptable and ethically preferable policies and practices. For example, some modes of transfer and some uses of human biological materials may be viewed as ethically preferable to others without those others being viewed as ethically unacceptable—for example, these traditions put a high premium on explicit gifts and donations without necessarily excluding tacit gifts, sales, abandonment, and appropriation in all cases (1).

The Impacts of These Religious Traditions

At least two major variables present in these religious traditions may affect the use of human biological materials: the **type or kind of materials** and the **mode of transfer.** The significance of different modes of transfer (or acquisition, if viewed from the standpoint of the user) and different materials will hinge on various moral principles, such as:

- respect for persons;
- beneficence, or benefiting others; and
- justice, or treating others fairly and distributing benefits and burdens equitable.

In addition, several other moral considerations, such as fidelity to promises and contracts, truthfulness, privacy, and confidentiality, might be derived from these general principles. From these principles and others, it is possible to indicate some judgments about the ethical acceptability and preferability of various policies.

According to the religious traditions analyzed, any of the following modes of transfer of human biological materials—gift (explicit or presumed), sale, abandonment, or appropriation—is ethically acceptable under some circumstances, but priority is given to explicit gifts. In any event, the first three modes of transfer all depend on voluntary, knowledgeable consent in significant, but different, ways. Thus, they all recognize some kind of property right by the original possessor of the biological materials. A recent prediction for future legislation is not surprising:

> Legislation in the future seems likely to follow an uneven course in which systems of voluntary consent will be diluted with mixtures of controlled commerce, contracting out, and limited compulsory acquisition (23).

SUMMARY AND CONCLUSIONS

Ethical choices about how to handle the transfers of human tissues and cells from patients and research subjects to physicians and researchers are important decisions in two respects. First, these choices will reflect the way in which the human body is regarded. If certain human parts are sacred or dignified, then social traditions suggest that they may be given, but not sold, and ownership of them is only of a special, limited kind.

Second, like the choice of how to obtain blood for transfusions, the system that is chosen for obtaining human tissues and cells will characterize relationships among the individuals of our society. These relationships are mediated through the profit and nonprofit institutions that connect human beings in their mutual quest to relieve suffering and to pursue the common good separately and together.

The dispute between those who believe that commercialization of the human body is justified and those who think it is not seems mostly to be an argument between those who accept a dualistic view of the separation between body (material, physiological being) and mind (immaterial, rational being), and those who do not. The former group includes theological and secular ethicists such as Joseph Fletcher. The latter include such theologians and secular philosophers as Paul Ramsey and Leon Kass. Others, such as H. Tristram Engelhardt, Jr., argue that commercialization must be tolerated as part of recognizing the limits of governmental authority to interfere in private choices, even on behalf of important goals or special beliefs certain groups may have about the sacred character of body parts that individuals may freely wish to sell.

Religious traditions offer insights about the value and significance of the human body. According to selected religious traditions, the human body is created in the image of God and therefore there are limits on what human beings can do with their own bodies and those of others. Although several methods of transferring human tissues and cells are acceptable within the Jewish, Catholic, and Protestant traditions, priority is given to explicit gifts.

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Appendixes

Appendix A

Code of Federal Regulations, Part 46, Subpart A: Basic Policy for Protection of Human Research Subjects, Department of Health and Human Services

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Reprinted below is Subpart A of the Department of Health and Human Services' regulations concerning basic protection of human research subjects. Other subparts, which are not reprinted here, address research involving fetuses, pregnant women, human in vitro fertilization, prisoners, and children.

46.101 To what do these regulations apply?
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46.103 Assurances
46.104-46.106 Reserved
46.108 IRB functions and operations
46.109 IRB review of research
46.110 Expedited review procedures for certain research
46.111 Criteria for IRB approval of research
46.112 Review by institution
46.113 Suspension or termination of IRB approval of research
46.114 Cooperative research
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46.119 Research undertaken without intention of involving humans
46.120 Evaluation and disposition of applications and proposals
46.121 Investigational new drug or device 30-day delay requirement
46.122 Use of Federal funds
46.123 Early termination of research funding
46.124 Conditions

§46.101 To what do these regulations apply?

(a) Except as provided in paragraph (b) of this section, this subpart applies to all research involving human subjects conducted by the Department of Health and Human Services or funded in whole or in part by a Department grant, contract, cooperative agreement or fellowship.

(1) This includes research conducted by Department employees, except each Principal Operating Component head may adopt such nonsubstantive, procedural modification as may be appropriate from an administrative standpoint.

(2) It also includes research conducted or funded by the Department of Health and Human Services outside the United States, but in appropriate circumstances, the Secretary may, under paragraph (e) of this section waive the applicability of some or all of the requirements of these regulations for research of this type.

(b) Research activities in which the only involvement of human subjects will be in one or more of the following categories are exempt from these regulations unless the research is covered by other subparts of this part:

(1) Research conducted in established or commonly accepted educational practices, such as (i) research on regular and special education instructional strategies, or (ii) research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

(2) Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), if information taken from these sources is recorded in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.

(3) Research involving survey or interview procedures, except where all of the following conditions exist: (i) Responses are recorded in such a manner that the human subjects can be identified, directly or through identifiers linked to the subjects; (ii) the subject's responses, if they became known outside the research, could reasonably place the subject at risk of criminal or civil liability

or be damaging to the subject's financial standing or employability; and (iii) the research deals with sensitive aspects of the subject's own behavior, such as illegal conduct, drug use, sexual behavior, or use of alcohol. All research involving survey or interview procedures is exempt, with exception, when the respondents are elected or appointed public officials or candidates for public office.

(4) Research involving the observation (including observation by participants) of public behavior, except where all of the following conditions exist: (i) Observations are recorded in such a manner that the human subjects can be identified, directly or through identifiers linked to the subjects; (ii) The observations recorded about the individual, if they became known outside the research, could reasonably place the subject at risk of criminal or civil liability or be damaging to the subject's financial standing or employability; and (iii) The research deals with sensitive aspects of the subject's own behavior such as illegal conduct, drug use, sexual behavior, or use of alcohol.

(5) Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.

(6) Unless specifically required by statute (and except to the extent specified in paragraph (i)), research and demonstration projects which are conducted by or subject to the approval of the Department of Health and Human Services, and which are designed to study, evaluate, or otherwise examine: (i) Programs under the Social Security Act, or other public benefit or service programs; (ii) Procedures for obtaining benefits or services under those programs; (iii) Possible changes in or alternatives to those programs or procedures; or (iv) Possible changes in methods or levels of payment for benefits or services under those programs.

(c) The Secretary has final authority to determine whether a particular activity is covered by these regulations.

(d) The Secretary may require that specific research activities conducted or funded by the Department, but not otherwise covered by these regulations, comply with some or all of these regulations.

(e) The Secretary may also waive applicability of these regulations to specific research activities or classes of research activities, otherwise covered by these regulations. Notices of these actions will be published in the *Federal Register* as they occur.

(f) No individual may receive Department funding for research covered by these regulations unless the individual is affiliated with or sponsored by an institution which assumes responsibility for the research under an assurance satisfying the requirements of this part, or the individual makes other arrangements with the Department.

(g) Compliance with these regulations will in no way render inapplicable pertinent Federal, state, or local laws or regulations.

(h) Each subpart of these regulations contains a separate section describing to what the subpart applies. Research which is covered by more than one subpart shall comply with all applicable subparts.

(i) If, following review of proposed research activities that are exempt from these regulations under paragraph (b)(6), the Secretary determines that a research or demonstration project presents a danger to the physical, mental, or emotional well-being of a participant or subject of the research or demonstration project, then Federal funds may not be expended for such a project without the written, informed consent of each participant or subject.

[46 FR 8386, Jan. 26, 1981; 46 FR 19195, Mar. 27, 1981, as amended at 48 FR 9269, Mar. 4, 1983]

§46.102 Definitions

(a) "Secretary" means the Secretary of Health and Human Services and any other officer or employee of the Department of Health and Human Services to whom authority has been delegated.

(b) "Department" or "HHS" means the Department of Health and Human Services.

(c) "Institution" means any public or private entity or agency (including Federal, state, and other agencies).

(d) "Legally authorized representative" means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedures) involved in the research.

(e) "Research" means a systematic investigation designed to develop or contribute to generalizable knowledge. Activities which meet this definition constitute "research" for purposes of these regulations, whether or not they are supported or funded under a program which is considered research for other purposes. For example, some "demonstration" and "service" programs may include research activities.

(f) "Human subject" means a living individual about whom an investigator (whether professional or student) conducting research obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information. "Intervention" includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes. "Interaction" includes communication or interpersonal contact between investigator and subject. "Private information" includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects.

(g) "Minimal risk" means that the risks of harm anticipated in the proposed research are not greater, considering probability and magnitude, than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or test.

(h) "Certification" means the official notification by the institution to the Department in accordance with the requirements of this part that a research project or activity involving human subjects has been reviewed and approved by the Institutional Review Board (IRB) in accordance with the approved assurance on file at HHS. (Certification is required when the research is funded by the Department and not otherwise exempt in accordance with §46.101(b).

[46 FR 8386, Jan. 26, 1981; 46 FR 19195, Mar. 27, 1981]

§46.103 Assurances

(a) Each institution engaged in research covered by these regulations shall provide written assurance satisfactory to the Secretary that it will comply with the requirements set forth in these regulations.

(b) The Department will conduct or fund research covered by these regulations only if the institution has an assurance approved as provided in this section, and only if the institution has certified to the Secretary that the research has been reviewed and approved by an IRB provided for in the assurance, and will be subject to continuing review by the IRB. This assurance shall at a minimum include:

(1) A statement of principles governing the institution in the discharge of its responsibilities for protecting the rights and welfare of human subjects of research conducted at or sponsored by the institution, regardless of source of funding. This may include an appropriate existing code, declaration, or statement of ethical principles, or a statement formulated by the institution itself. This requirement does not preempt provisions of these regulations applicable to Department-funded research and is not applicable to any research in an exempt category listed in §46.101.

(2) Designation of one or more IRBs established in accordance with the requirements of this subpart, and for which provisions are made for meeting space and sufficient staff to support the IRBs review and recordkeeping duties.

(3) A list of the IRB members identified by name; earned degrees; representative capacity; indications of experience such as board certifications, licenses, etc., sufficient to describe each member's chief anticipated contributions to IRB deliberations; and any employment or other relationship between each member and the institution; for example: full-time employee, part-time employee, member of governing panel or board, stockholder, paid or unpaid consultant. Changes in IRB membership shall be reported to the Secretary.

(4) Written procedures which the IRB will follow (i) for conducting its initial and continuing review of research and for reporting its findings and actions to the investigator and the institution; (ii) for determining which projects require review more often than annually and which projects need verification from sources other than the investigators that no material changes have occurred since previous IRB review; (iii) for insuring prompt reporting to the IRB of proposed changes in a research activity, and for insuring that changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except where necessary to eliminate apparent immediate hazards to the subject; and (iv) for insuring prompt reporting to the IRB and to the Secretary of unanticipated problems involving risks to subjects or others.

(c) The assurance shall be executed by an individual authorized to act for the institution and to assume on behalf of the institution the obligations imposed by these regulations, and shall be filed in such form and manner as the Secretary may prescribe.

(d) The Secretary will evaluate all assurances submitted in accordance with these regulations through such officers and employees of the Department and such experts or consultants engaged for this purpose as the Secretary determines to be appropriate. The Secretary's evaluation will take into consideration the adequacy of the proposed IRB in light of the anticipated scope of the institution's research activities and the types of subject populations likely to be involved, the appropriateness of the proposed initial and continuing review procedures in light of the probable risks, and the size and complexity of the institution.

(e) On the basis of this evaluation, the Secretary may approve or disapprove the assurance, or enter into negotiations to develop an approvable one. The Secretary may limit the period during which any particular approved assurance shall remain effective or otherwise condition or restrict approval.

(f) Within 60 days after the date of submission to HHS of an application or proposal, an institution with an approved assurance covering the proposed research shall certify that the application or proposal has been approved by the IRB within 30 days after receipt of a request for such a certification from the Department. If the certification is not submitted within these time limits, the application or proposal may be returned to the institution.

§§46.104-46.106 [Reserved]

(a) Each IRB shall have at least five members, with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution. The IRB shall be sufficiently qualified through the experience and expertise of its members, and the diversity of the members' backgrounds including consideration of the racial and cultural backgrounds of members and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects. In addition to possessing the professional competence necessary to review specific research activities, the IRB shall be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice. The IRB shall therefore include persons knowledgeable in these areas. If an IRB regularly reviews research that involves a vulnerable category of subjects, including but not limited to subjects covered by other subparts of this part, the IRB shall include one or more individuals who are primarily concerned with the welfare of these subjects.

(b) No IRB may consist entirely of men or entirely of women, or entirely of members of one profession.

(c) Each IRB shall include at least one member whose primary concerns are in nonscientific areas; for example: lawyers, ethicists, members of the clergy.

(d) Each IRB shall include at least one member who is not otherwise affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution.

(e) No IRB may have a member participating in the IRBs initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB.

(f) An IRB may, in its discretion, invite individuals with competence in special areas to assist in the review of complex issues which require expertise beyond or in addition to that available on the IRB. These individuals may not vote with the IRB.

§46.108 IRB functions and operations

In order to fulfill the requirements of these regulations each IRB shall:

(a) Follow written procedures as provided in §46.103(b)(4).

(b) Except when an expedited review procedure is used (see §46.110), review proposed research at convened meetings at which a majority of the members of the IRB are present, including at least one member whose primary concerns are in nonscientific areas. In order for the research to be approved, it shall receive the approval of a majority of those members present at the meeting.

(c) Be responsible for reporting to the appropriate institutional officials and the Secretary any serious or continuing noncompliance by investigators with the requirements and determinations of the IRB.

[46 FR 8386, Jan. 26, 1981; 46 FR 19195, Mar. 27, 1981]

§46.109 IRB review of research

(a) An IRB shall review and have authority to approve, require modifications in (to secure approval), or disapprove all research activities covered by these regulations.

(b) An IRB shall require that information given to subjects as part of informed consent is in accordance with §46.116. The IRB may require that information, in addition to that specifically mentioned in §46.116, be given to the subjects when in the IRB's judgment the information would meaningfully add to the protection of the rights and welfare of subjects.

(c) An IRB shall require documentation of informed consent or may have documentation in accordance with §46.117.

(d) An IRB shall notify investigators and the institution in writing of its decision to approve or disapprove the proposed research activity, or of modifications required to secure IRB approval of the research activity. If the IRB decides to disapprove a research activity, it shall include in its written notification a statement of the reasons for its decision and give the investigator an opportunity to respond in person or in writing.

(e) An IRB shall conduct continuing review of research covered by these regulations at intervals appropriate to the degree of risk, but not less than once per year, and shall have authority to observe or have a third party observe the consent process and the research.

§46.110 Expedited review procedures for certain kinds of research involving no more than minimal risk, and for minor changes in approved research

(a) The Secretary has established, and published in the *Federal Register*, a list of categories of research that may be reviewed by the IRB through an expedited review procedure. The list will be amended, as appropriate, through periodic republication in the *Federal Register*.

(b) An IRB may review some or all of the research appearing on the list through an expedited review procedure, if the research involves no more than minimal risk. The IRB may also use the expedited review procedure to review minor changes in previously approved research during the period for which approval is authorized. Under an expedited review procedure, the review may be carried out by the IRB chairperson or by one or more experienced reviewers designated by the chairperson from among members of the IRB. In reviewing the research, the reviewers may exercise all of the authorities of the IRB except that the reviewers may not disapprove the research. A research activity may be disapproved only after review in accordance with the non-expedited procedure set forth in §46.108(b).

(c) Each IRB which uses an expedited review procedure shall adopt a method for keeping all members advised of research proposals which have been approved under the procedure.

(d) The Secretary may restrict, suspend, or terminate an institution's or IRBs use of the expedited review procedure when necessary to protect the rights or welfare of subjects.

§46.111 Criteria for IRB approval of research

(a) In order to approve research covered by these regulations the IRB shall determine that all of the following requirements are satisfied:

(1) Risks to subjects are minimized: (i) By using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

(2) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.

(3) Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted.

(4) Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by §46.116.

(5) Informed consent will be appropriately documented, in accordance with, and the extent required by §46.117.

(6) Where appropriate, the research plan makes adequate provision for monitoring the data collected to insure the safety of subjects.

(7) Where appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

(b) Where some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as persons with acute or severe physical or mental illness, or persons who are economically or educationally disadvantaged, appropriate additional safeguards have been included in the study to protect the rights and welfare of these subjects.

§46.112 Review by institution

Research covered by these regulations that has been approved by an IRB may be subject to further appropriate review and approval or disapproval by officials of the institution. However, those officials may not approve the research if it has not been approved by an IRB.

§46.113 Suspension or termination of IRB approval of research

An IRB shall have authority to suspend or terminate approval of research that is not being conducted in accordance with the IRBs requirements or that has been associated with unexpected serious harm to subjects. Any suspension or termination of approval shall include a statement of the reasons for the IRBs action and shall be reported promptly to the investigator, appropriate institutional officials, and the Secretary. [46 FR 8386, Jan. 26, 1981; 46 FR 19195, Mar. 27, 1981]

§46.114 Cooperative research

Cooperative research projects are those projects, normally supported through grants, contracts, or similar arrangements, which involve institutions in addition to the grantee or prime contractor (such as a contractor with the grantee, or a subcontractor with the prime contractor). In such instances, the grantee or prime contractor remains responsible to the Department for safeguarding the rights and welfare of human subjects. Also, when cooperating institutions conduct some or all of the research involving some or all of these subjects, each cooperating institution shall comply with these regulations as though it received funds for its participation in the project directly from the Department, except that in complying with these regulations institutions may use joint review, reliance upon the review of another qualified IRB, or similar arrangements aimed at avoidance of duplication of effort.

§46.115 IRB records

(a) An institution, or where appropriate an IRB, shall prepare and maintain adequate documentation of IRB activities, including the following:

(1) Copies of all research proposals reviewed, scientific evaluations, if any, that accompany the proposals, approved sample consent documents, progress reports submitted by investigators, and reports of injuries to subjects.

(2) Minutes of IRB meetings which shall be in sufficient detail to show attendance at the meetings; actions taken by the IRB; the vote on these actions including the number of members voting for, against, and abstaining; the basis of requiring changes in or disapproving research; and a written summary of the discussion of controverted issues and their resolution.

(3) Records of continuing review activities.

(4) Copies of all correspondence between the IRB and the investigators.

(5) A list of IRB members as required by §46.103(b)(3).

(6) Written procedures for the IRB as required by §46.103(b)(4).

(7) Statements of significant new findings provided to subjects, as required by §46.116(b)(5).

(b) The records required by this regulation shall be retained for at least 3 years after completion of the research, and the records shall be accessible for inspection and copying by authorized representatives of the Department at reasonable times and in a reasonable manner.

[46 FR 8386 Jan. 26, 1981; 46 FR 19195, Mar. 27, 1981]

§46.115 General requirements for informed consent

Except as provided elsewhere in this or other subparts, no investigator may involve a human being as a subject in research covered by these regulations unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The information that is given to the subject or the representative shall be in language understandable to the subject or the representative. No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence.

(a) Basic elements of informed consent. Except as provided in paragraph (c) or (d) of this section, in seeking informed consent the following information shall be provided to each subject:

(1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental;

(2) A description of any reasonably foreseeable risks or discomforts to the subject;

(3) A description of any benefits to the subject or to others which may reasonably be expected from the research;

(4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject;

(5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained;

(6) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained;

(7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject; and

(8) A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

(b) Additional elements of informed consent. When appropriate, one or more of the following elements of information shall also be provided to each subject:

(1) A statement that the particular treatment or procedure may involve risks to the subject (or to

the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable;

(2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent;

(3) Any additional costs to the subject that may result from participation in the research;

(4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject;

(5) A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject; and

(6) The approximate number of subjects involved in the study.

(c) An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth above, or waive the requirement to obtain informed consent provided the IRB finds and documents that:

(1) The research or demonstration project is to be conducted by or subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine: (i) Programs under the Social Security Act, or other public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs; and

(2) The research could not practicably be carried out without the waiver or alteration.

(d) An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth above, or waive the requirements to obtain informed consent provided the IRB finds documents that:

(1) The research involves no more than minimal risk to the subjects;

(2) The waiver or alteration will not adversely affect the rights and welfare of the subjects;

(3) The research could not practicably be carried out without the waiver or alteration; and

(4) Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

(e) The informed consent requirements in these regulations are not intended to preempt any applicable Federal, state, or local laws which require additional information to be disclosed in order for informed consent to be legally effective.

(f) Nothing in these regulations is intended to limit the authority of a physician to provide emergency medical care, to the extent the physician is permitted to do so under applicable Federal, state, or local law.

[46 FR 8386, Jan. 26, 1981; 46 FR 29883, June 3, 1981, as amended at 48 FR 9270, Mar. 4, 1983]

§46.117 Documentation of informed consent

(a) Except as provided in paragraph (c) of this section, informed consent shall be documented by the use of a written consent form approved by the IRB and signed by the subject or the subject's legally authorized representative. A copy shall be given to the person signing the form.

(b) Except as provided in paragraph (c) of this section, the consent form may be either of the following:

(1) A written consent document that embodies the elements of informed consent required by §46.116. This form may be read to the subject or the subject's legally authorized representative, but in any event, the investigator shall give either the subject or the representative adequate opportunity to read it before it is signed; or

(2) A "short form" written consent document stating that the elements of informed consent required by §46.116 have been presented orally to the subject or the subject's legally authorized representative. When this method is used, there shall be a witness to the oral presentation. Also, the IRB shall approve a written summary of what is to be said to the subject or the representative. Only the short form itself is to be signed by the subject or the representative. However, the witness shall sign both the short form and a copy of the summary, and the person actually obtaining consent shall sign a copy of the summary. A copy of the summary shall be given to the subject or the representative, in addition to a copy of the "short form."

(c) An IRB may waive the requirement for the investigator to obtain a signed consent form for some or all subjects if it finds either:

(1) That the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern; or

(2) That the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.

In cases where the documentation requirement is waived, the IRB may require the investigator to provide subjects with a written statement regarding the research.

§46.118 Applications and proposals lacking definite plans for involvement of human subjects

Certain types of applications for grants, cooperative agreements, or contracts are submitted to the Department with the knowledge that subjects may be involved within the period of funding, but definite plans would not normally be set forth in the application or proposal. These include activities such as institutional type grants (including bloc grants) where selection of specific projects is the institution's responsibility; research training grants where the activities involving subjects remain to be selected; and projects in which human subjects' involvement will depend upon completion of instruments, prior animal studies, or purification of compounds. These applications need not be reviewed by an IRB before an award may be made. However, except for research described in §46.101(b), no human subjects may be involved in any project supported by these awards until the project has been reviewed and approved by the IRB, as provided in these regulations, and certification submitted to the Department.

§46.119 Research undertaken without the intention of involving human subjects

In the event research (conducted or funded by the Department) is undertaken without the intention of involving human subjects, but it is later proposed to use human subjects in the research, the research shall first be reviewed and approved by an IRB, as provided in these regulations, a certification submitted to the Department, and final approval given to the proposed change by the Department.

§46.120 Evaluation and disposition of applications and proposals

(a) The Secretary will evaluate all applications and proposals involving human subjects submitted to the Department through such officers and employees of the Department and such experts and consultants as the Secretary determines to be appropriate. This evaluation will take into consideration the risks to the subjects, the adequacy of protection against these risks, the potential benefits of the proposed research to the subjects and others, and the importance of the knowledge to be gained.

(b) On the basis of this evaluation, the Secretary may approve or disapprove the application or proposal, or enter into negotiations to develop an approvable one.

§46.121 Investigational new drug or device 30-day delay requirement

When an institution is required to prepare or to submit a certification with an application or proposal under these regulations, and the application or proposal involves an investigational new drug (within the meaning of 21 U.S.C. 355(i) or 357(d)) or a significant risk device (as defined in 21 CFR 812.3(m)), the institution shall identify the drug or device in the certification. The institution shall also state whether the 30-day interval required for investigational new drugs by 21 CFR 312.1(a) and for significant risk devices by 21 CFR 812.30 has elapsed, or whether the Food and Drug Administration has requested that the sponsor continue to withhold or restrict the use of the drug or device in human subjects. If the 30-day interval has not expired, and a waiver has not been received, the institution shall send a statement to the Department upon expiration of the interval. The Department will not consider a certification acceptable until the institution has submitted a statement that the 30-day interval has elapsed, and the Food and Drug Administration has not requested it to limit the use of the drug or device, or that the Food and Drug Administration has waived the 30-day interval.

§46.122 Use of Federal funds

Federal funds administered by the Department may not be expended for research involving human subjects unless the requirements of these regulations, including all subparts of these regulations, have been satisfied.

§46.123 Early termination of research funding: evaluation of subsequent applications and proposals

(a) The Secretary may require that Department funding for any project be terminated or suspended in the manner prescribed in applicable program requirements, when the Secretary finds an institution has materially failed to comply with the terms of these regulations.

(b) In making decisions about funding applications or proposals covered by these regulations, the Secretary may take into account, in addition to all other eligibility requirements and program criteria, factors such as whether the applicant has been subject to a termination or suspension under paragraph (a) of this section and whether the applicant or the person who would direct the scientific and technical aspects of an activity has in the judgment of the Secretary materially failed to discharge responsibility for the protection of the rights and welfare of human subjects (whether or not Department funds were involved).

§46.124 Conditions

With respect to any research project or any class of research projects the Secretary may impose additional conditions prior to or at the time of funding when in the Secretary's judgment additional conditions are necessary for the protection of human subjects.

Appendix B

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Leonard H. Glantz
Boston University School of Public Health

John H. Goddeeris
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Richard D. Godown
Industrial Biotechnology Association

Leonard H. Glantz
Boston University School of Public Health

David W. Golde
University of California, Los Angeles

Susanne M. Gollin
University of Arkansas for the Medical Sciences

Zsolt Harsanyi
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Clark B. Inderlied
University of Southern California

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The University of California at San Francisco

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Appendix C

Glossary

Abandonment: The surrender, relinquishment, disclaimer, or cession of property or rights.

Accession: Coming into possession of a right or office, including the right to all that one's own property produces, whether that property be movable or immovable.

Actionable: Furnishing legal ground for a proceeding in a court of justice.

Amino acid: One of 20 molecules that are linked together in various combinations to form proteins. Each different protein is made up of a specific sequence of these molecules with the unique sequence coded for by DNA.

Aneuploid: An abnormal number—either an excess or deficiency—of chromosomes in a cell. *See* diploid.

Antibody: A protein molecule, also called immunoglobulin, produced by the immune system in response to exposure to a foreign substance. An antibody is characterized by a structure complementary to the foreign substance, the antigen, that provoked its formation and is thus capable of binding specifically to the foreign substance to neutralize it. *See* antigen and monoclonal antibodies.

Antigen: A molecule introduced into an organism and recognized as a foreign substance, resulting in the elicitation of an immune response (antibody production, lymphokine production, or both) directed specifically against that molecule. *See* antibody and monoclonal antibodies.

Autoimmune disease: A disease in which the body's defenses (its immune system) fail to distinguish the body's own tissue from foreign matter with the result that the body's own tissue is attacked and damaged.

Autonomy: Derived from the Greek "autos" (self) and "nomos" (rule, governance, or law), first used in reference to self-rule or self-governance in Greek city-states. In ethics, it is the principle that independent actions and choices of an individual should not be constrained by others.

B lymphocyte: A specialized white blood cell involved in the immune response of vertebrates that originates in the bone marrow and produces antibody molecules after challenge by an antigen. In hybridoma technology, these cells contribute antibody-producing capability to a hybridoma. *See* T lymphocyte.

Beneficence: Mercy, kindness, or charity. In ethics, it is the principle that one has a duty to confer benefits or to help others further their legitimate interests.

Cell: The smallest component of life capable of carrying on all essential life processes. A single unit is a complex collection of molecules with many different activities all integrated to form a functional self-assembling, self-regulating, self-reproducing biological unit. *See* eukaryote and prokaryote.

Cell culture: The propagation of cells removed from organisms in a laboratory environment that has strict sterility, temperature, and nutrient requirements; also used to refer to any particular individual sample. *See* cell and cell line.

Cell line: A sample of cells that has undergone the process of adaptation to artificial laboratory cultivation and is capable of sustaining continuous, long-term growth in culture. *See* cell and cell culture.

Chattel: An article of personal property, more comprehensive than "goods" because it includes animate as well as inanimate property.

Chromosome: The physical, threadlike structure within the nucleus of a cell composed of a DNA-protein complex and containing the hereditary material, i.e., genes. In bacteria, it is the DNA molecule—a single, closed circle (no associated protein)—comprising the cell's total genetic information.

Cloning: The process of asexually producing many copies of a biological material, all identical to the original ancestor. In tissue and cell culture technology, the process by which a culture is grown and amplified starting from a single cell; in recombinant DNA technology, the process of using a variety of recombinant DNA procedures to produce multiple copies of a single gene or segment of DNA.

Common law: Law created by judicial decisions, as distinguished from law created by the enactments of legislatures. In the United States, common law encompasses that portion of the common law of England (including such acts of parliament as were applicable) that had been adopted and was in force here at the time of the American Revolution.

Conversion: Any unauthorized interference in the right of ownership over goods or personal chattels belonging to another resulting in the alteration of their condition or the exclusion of the owner's rights; any unauthorized act that deprives an owner of his property permanently or for an indefinite period of time.

Deoxyribonucleic acid: *See* DNA.

Diploid: The state of having two complete sets of match-paired chromosomes—one set of paternal origin, the other of maternal origin—in all normal cells in higher organisms, except sex cells. In normal human cells, this number is 46. *See* aneuploid.

Distributive justice: Theories and principles for the fair allocation of resources in general and scarce resources in particular. *See* justice.

DNA (deoxyribonucleic acid): The molecule that is the repository of genetic information in all organisms (with the exception of a small number of viruses in which the hereditary material is ribonucleic acid—RNA). The information coded by DNA determines the structure and function of an organism.

Enzyme: A protein that acts as a catalyst, speeding the rate at which a biochemical reaction proceeds, but not altering its direction or nature.

Equity: Fairness and equality. In economics, the monetary value of a proper , or of an interest in a property, in excess of claims or liens against it. In law, a body of law separate from common law that is designed to achieve a lawful result when legal procedure is inadequate.

Eukaryote: An organism with well-developed organelles and whose genetic material (DNA) is enclosed within membrane-bound, structurally discrete nuclei. Eukaryotes include all organisms except viruses, bacteria, and blue-green algae. *See* prokaryote.

Exculpatory: Clearing or tending to clear from alleged fault or guilt; excusing.

Fiduciary: Of or founded in confidence or trust; also a person having a duty to act in scrupulous good faith primarily for another's benefit.

For-profit: Referring to an organization primarily designed to pay dividends on invested capital; an institution organized to yield an excess of returns over expenditures. *See* nonprofit.

Gene: The fundamental unit of heredity; an ordered sequence of nucleotide base pairs which produce a specific product or have an assigned function.

Gene probe: A molecule of known structure or function, labeled with a tracer substance such as a dye or radioactive label, that is used to locate and identify a specific region or base sequence of DNA or RNA. In this report, a gene probe as an end product refers to a cloned DNA sequence.

Host: In recombinant DNA technology, the organism used for growth and reproduction of virus, plasmid, or other foreign DNA.

Hybridization: In cell culture, the formation of new cells as a result of the fusion of whole cells or cell parts of different parental origin. In recombinant DNA, a procedure in which single-stranded nucleic acid segments are allowed to bind to identical or nearly identical sequences, forming hybrid double-stranded helices.

Hybridoma: A new cell resulting from the fusion of a particular type of immortal tumor cell line, a myeloma, with an antibody-producing B lymphocyte. Cultures of such cells are capable of continuous growth and specific (i.e., monoclonal) antibody production.

Imago dei: From Latin, meaning in the image of God.

Immunization: The injection of an antigen into an organism resulting in an immune response that may include the production of antibodies.

Immunoglobulin: *See* antibody.

In vitro: Literally, "in glass." Refers to a process, test, or procedure in which something is measured, observed, or produced outside a living organism after extraction from the organism. *See* in vivo.

In vivo: Literally, "in the living." Refers to a reaction that is being observed or investigated using an intact organism. *See* in vitro.

Justice: Generally refers to fair and equal treatment. In ethics, it is the principle that one should act in such a manner that no one person bears a disproportionate share of benefits or burdens. *See* distributive justice.

Lymphocytes: *See* B lymphocyte *and* T lymphocyte.

Lymphokine: A group of proteins that modulate the immune response and that are necessary for proper function of the entire immune system. Interferon and interleukin-2 are lymphokines.

Macrophage: A large specialized cell that originates in the bone marrow and is involved in many stages of the immune response, including consumption of foreign particles such as viruses and lymphokine production.

Market: The available supply of or potential demand for specified goods or services.

Monoclonal antibodies: Identical antibodies that recognize a single, specific antigen and are produced by a clone of specialized cells. Commercial quantities of these molecules are now produced by hybridomas. *See* antibody, antigen, *and* hybridoma.

Myeloma: A malignant tumor of an antibody-producing cell. In hybridoma technology, some of these tumor cells have been adapted to cell culture, and these cells contribute immortality to a hybridoma cell line.

Nonmaleficence: Generally associated with the maxim *"primum non nocere"*—from Latin, meaning above all, do no harm. In ethics, it is the principle that one has a duty not to inflict evil, harm, or risk of harm.

Nonprofit: Referring to an organization primarily designed not to pay dividends on invested capital; an organization not conducted or maintained for the purpose of yielding an excess of returns over expenditures in a transaction or series of transactions. *See* for-profit.

Nucleus: The membrane-enclosed structure in eukaryotes that contains the chromosomes.

Organelle: A structure outside the nucleus of a cell that is specialized in its ultrastructure and biochemical composition to serve a particular function (e.g., mitochondria, endoplasmic reticulum, chloroplast).

Pathogenic: Able to cause disease; often used to express lethality.

Prokaryote: An organism lacking organelles and in which the genetic material (DNA or RNA) is not enclosed within a membrane-bound, structurally discrete nucleus. Bacteria and blue-green algae are prokaryotes. *See* eukaryote.

Protein: A molecule composed of a few to hundreds of amino acids linked in a specific sequence determined by the sequence of a gene in the DNA. These molecules are required for the structure and function of all living organisms.

Recombinant DNA: A broad range of techniques involving the manipulation of the genetic material of organisms; often used synonymously with genetic engineering; also used to describe a DNA molecule constructed by genetic engineering techniques and composed of DNA from different individuals or species.

Res nullius: The property of no one. A thing which has no owner, either because a former owner has finally abandoned it, because it has never been appropriated by any person, or because it is not susceptible to private ownership.

Restriction endonuclease: An enzyme isolated from bacteria that selectively recognizes and clips double-stranded DNA at specific sequences. More than 400 different restriction enzymes are known to recognize over 100 different DNA sequences.

Restriction enzyme: *See* restriction endonuclease.

Ribonucleic acid: *See* RNA.

RNA (ribonucleic acid): A molecule existing in three forms—messenger RNA, transfer RNA, and ribosomal RNA—responsible for translating the genetic information encoded by an organism (i.e., DNA) into a protein product; the hereditary material of some viruses.

Somatic: Pertaining to the cells of an organism except for those of the germ line (i.e., sex cells—sperm and eggs).

Specification: In law, relating to patents, machinery, and building contracts, a particular or detailed statement of the various elements involved.

Statute: A law enacted and established by the legislative branch of the government.

T lymphocyte: Specialized white blood cell involved in the immune response of vertebrates that originates in the bone marrow, matures in the thymus gland, and produces some lymphokines. Subclasses of T lymphocytes are important to antibody production and the enhancement or suppression of an immune response. *See* B lymphocyte *and* macrophage.

Tissue culture: *See* cell culture.

Tort law: Derived from legal principles governing wrongful acts, except those involving a breach of contract, committed against a person or property for which civil action will be valid.

Transaction cost: An outlay associated with carrying out a business deal.

Undue influence: Any improper constraint on a person particularly susceptible to persuasion which deprives the person being influenced from acting with free will.

Uniform Commercial Code (UCC): A model act, begun in 1942 by the American Law Institute and the National Conference of Commissioners, to replace most existing statutes relating to commercial transactions. Adopted in part or whole by every State.

Vector: A DNA molecule used to introduce foreign DNA into host cells.

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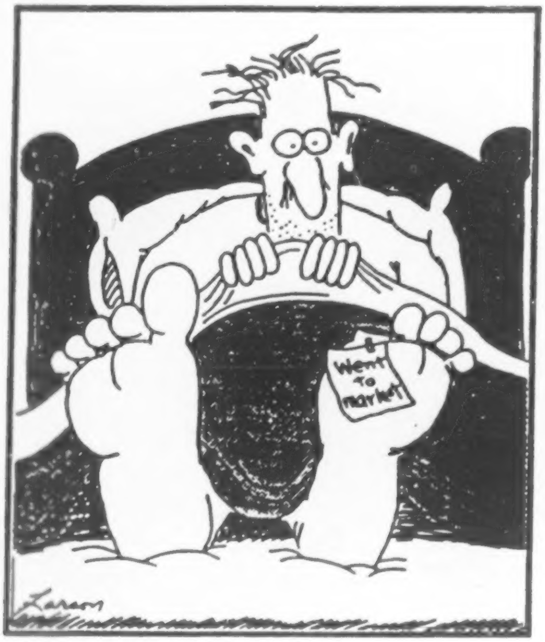
Went
To
market
Larson

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Office of Technology Assessment

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